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PRIORITY SUBSTANCES LIST

STATE OF THE SCIENCE REPORT

for

ETHYLENE GLYCOL

Environment Canada
Health Canada

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LIST OF ACRONYMS AND ABBREVIATIONS

ATAC	Air Transport Association of Canada
BMD_{05}	Benchmark $Dose_{05}$; the dose estimated to cause a 5% increase in incidence over the background response rate
BOD	biological oxygen demand
CAS	Chemical Abstracts Service
CCME	Canadian Council of Ministers of the Environment
CEPA	*Canadian Environmental Protection Act*
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CTV	Critical Toxicity Value
DL	detection limit
DO	dissolved oxygen
EC_{25}	effective concentration for 25% of the test population
EC_{50}	median effective concentration
EEV	Estimated Exposure Value
EG	ethylene glycol
ENEV	Estimated No-Effects Value
GMP	glycol mitigation plan
GOMP	glycol operational management plan
GWP	Global Warming Potential
HVAC	heating, ventilation and air conditioning
IC_{25}	inhibiting concentration for a 25% effect
IC_{50}	inhibiting concentration for a 50% effect
kg-bw	kilogram body weight
K_{ow}	octanol/water partition coefficient
LC_{25}	lethal concentration resulting in 25% mortality
LC_{50}	lethal concentration resulting in 50% mortality
95% LCL	lower 95% confidence limit of the BMD_{05}
LD_{50}	median lethal dose
LOEC	Lowest-Observed-Effect Concentration
LOED	Lowest-Observed-Effect Dose
LOEL	Lowest-Observed-Effect Level
MWTP	municipal wastewater treatment plant
NAP	National Airports Policy
NAS	National Airports System
NATES	National Analysis of Trends in Emergency Systems
NOAEL	No-Observed-Adverse-Effect Level
NOEC	No-Observed-Effect Concentration
NOEL	No-Observed-Effect Level
NPRI	National Pollutant Release Inventory
ODP	Ozone Depletion Potential

PETE	polyethylene terephthalate
POCP	Photochemical Ozone Creation Potential
PSL	Priority Substances List
RCF	regenerated cellulose film

SYNOPSIS

Ethylene glycol (CAS No. 107-21-1) is a colourless, odourless, relatively non-volatile liquid. It has a low vapour pressure and is completely miscible in water.

Ethylene glycols (mono-, di- and tri-) are produced by three companies in Canada, which had a total annual capacity of 850 kilotonnes in 1996. Ethylene glycol is used primarily as an antifreeze agent but is also used, for example, in the manufacture of polyethylene terephthalate, in natural gas processing and as a component of paints. Natural levels of ethylene glycol are considered to be insignificant relative to amounts released from anthropogenic sources. The highest reported releases of ethylene glycol to the environment are to land from aircraft deicing/anti-icing operations, with subsequent release to the aquatic environment. Current management practices at the major airports in Canada have resulted in a trend of decreased releases in recent years. Other sources of releases to water include paper products and steel industries. Releases to air occur during ethylene glycol production, during natural gas processing and from paints and coatings manufacture. Ethylene glycol is also injected underground as a means of disposal from natural gas processing operations.

Once released into the environment, ethylene glycol partitions mainly into surface water or groundwater. It does not bioaccumulate or persist in the environment, primarily due to biodegradation. Half-lives in air, water, groundwater and soil are estimated to typically range from 0.35 to 3.5 days, from 2 to 12 days, from 4 to 24 days, and from 2 to 12 days, respectively, but may exceed these ranges, depending on the environmental conditions. Ethylene glycol is not expected to deplete the ozone layer, it has a low potential to contribute to ground-level ozone formation, and its potential contribution to climate change is negligible. Ethylene glycol has been found to biodegrade rapidly in the aquatic environment and therefore has the potential to induce depletion of the dissolved oxygen (DO) in receiving waters.

Given that ethylene glycol tends to partition to the aquatic environment, with little transfer to soil or air expected, and because the majority of ethylene glycol is released to the aquatic environment from aircraft deicing and anti-icing, the potential for effects is greatest for aquatic organisms. In assessing the risk, consideration is given to the time and frequency of exposure. From the available studies, the induction of effects on algae and amphibians is selected to represent the most sensitive measurement endpoints for inducing potential population-level impacts on aquatic organisms and is used as a basis for generating the Estimated No-Effects Values (ENEVs). Indirect effects from oxygen depletion following ethylene glycol release was also examined using the Streeter-Phelps oxygen sag model and probabilistic analysis.

The direct comparison of current exposure concentrations predicted to occur in the aquatic environment with the ENEVs suggests that adverse effects are unlikely when consideration is given to the seasonal nature of releases, ambient temperatures, metabolic rates and duration of exposure. Examination of potential indirect effects through oxygen depletion suggests a low potential for DO levels to drop below the Canadian water quality guideline (9.5 mg/L) under very infrequent, maximal loading

conditions. Although, based on the present characterization, it is evident that harmful environmental effects are unlikely to result from exposure to ethylene glycol in Canada, effects related to depletion of DO levels in receiving waters are possible under conditions of maximum loading at some Canadian airports. It is therefore recommended that current efforts to reduce releases of ethylene glycol during aircraft deicing/anti-icing operations (e.g., glycol mitigation plans and glycol operational management plans) continue to be strengthened, with the aim of reducing further the instances when ethylene glycol concentrations in stormwaters exceed the CEPA effluent guideline of 100 mg total glycol/L.

Monitoring data upon which to base estimates of exposure of the general human population in Canada to ethylene glycol were not identified. Population exposure estimates are, therefore, extremely limited. Intakes in air and soil in the vicinity of a point source were estimated based on modelled data, and that in food was based on reported concentrations in a limited range of foodstuffs from other countries. Dermal absorption was also estimated for a limited range of products for which data on the proportion of ethylene glycol in the product were identified.

Based on short-term and long-term studies conducted by the oral route in experimental animals, the kidney is the principal target site for effects of ethylene glycol. Consistently, degenerative non-neoplastic changes in the kidney have been observed at lowest doses in a range of species. Based on an extensive database, ethylene glycol induces slight reproductive effects and developmental toxicity, including teratogenicity, in rodents exposed by the oral route, although at doses greater than those associated with renal effects.

Therefore, a Tolerable Intake has been derived for this substance, based on a Benchmark Dose calculated for non-neoplastic renal effects in animals and an uncertainty factor. However, owing to limitations of available studies, this Tolerable Intake is uncertain. Based on highly uncertain estimates, exposure of some age groups in the vicinity of a point source or of adults through absorption from some consumer products exceeds the Tolerable Intake. A Tolerable Intake is the level of intake to which it is believed a person may be exposed daily over a lifetime without deleterious effect. To reduce the considerable uncertainty, in critical areas, research on exposure in the vicinity of point sources and progression of renal lesions in toxicity studies is considered a priority. Characterization of the distribution and ranges of ethylene glycol in consumer products in Canada is also recommended.

1.0 INTRODUCTION

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) requires the federal Ministers of the Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health.

Based on initial screening of readily accessible information, the rationale for including ethylene glycol provided by the Ministers' Expert Advisory Panel on the Second Priority Substances List (Ministers' Expert Advisory Panel, 1995) was as follows:

> Large volumes of ethylene glycol are used in heat transfer fluids (including automotive antifreeze), aircraft de-icers and in the manufacture of polyesters. Exposure to concentrations that approach those inducing developmental effects in animals may occur through the use of latex paint. The Panel noticed that risk management programs have already been implemented to reduce risks to aquatic ecosystems from the use of de-icing fluids at federally operated airports. An assessment is needed to address potential health concerns from exposure to ethylene glycol in the environment.

The search strategies employed in the identification of data relevant to the characterization of potential effects on the environment (prior to October 1999) and human health (prior to January 2000) are presented in Appendix A. Review articles were consulted where appropriate. However, all original studies that form the basis for this State of the Science Report have been critically evaluated by staff of Environment Canada (entry and environmental exposure and effects) and Health Canada (human exposure and effects on human health).

Preparation of sections of this Report and Supporting Documentation relevant to the environmental part of this report (Environment Canada, 2000) was coordinated and led by M. Lewis of Environment Canada, and an initial draft was prepared by D. Moore and S. Teed of The Cadmus Group Inc. with direct input from the Guidelines and Standards Division of the Ecosystem Science Directorate of Environment Canada. An Environmental Resource Group was established by Environment Canada to assist in the preparation of the environmental characterization. Members were selected based on their expertise and interest in the substance. The assistance and information provided by the Environmental Resource Group members who participated in the preparation and review of this Report and environmental Supporting Document are gratefully acknowledged. These individuals include:

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Environmental sections of this Report and the environmental Supporting Document were also reviewed by K. Lloyd and P. Doyle from Environment Canada, as well as by external reviewers:

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The health-related sections of this Report and Supporting Documentation (Health Canada, 2000) were prepared by the following staff of Health Canada:

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Studies relating to dermal absorption relevant to this Report were reviewed by R. Moody of the Product Safety Bureau of Health Canada. Advice on interpretation of histopathological lesions reported in critical studies was provided by D. Wolf, National Health and Environmental Effects Research Laboratory, U.S. Environmental Protection Agency, and R. Maronpot, U.S. National Institute of Environmental Health Sciences and National Toxicology Program. M. Wade, Environmental and Occupational Toxicology Division of Health Canada, contributed to the interpretation of data on reproductive/developmental toxicity. Statistical support was provided by M. Walker of Health Canada. Sections of the Supporting Documentation pertaining to human health were reviewed externally by the Ethylene Glycol Panel of the Chemical Manufacturers Association, primarily to address adequacy of coverage. Members of the panel included W. Snellings, Union Carbide Corporation, W. Faber, Eastman Kodak, R. Gingell, Shell Chemical Company, and S. Jasti, BASF Corporation.

Accuracy of reporting, adequacy of coverage and defensibility of conclusions with respect to hazard characterization and exposure–response analyses were considered at a panel meeting of the following members, convened by Toxicology Excellence in Risk Assessment (TERA), on February 14, 2000, in Ottawa, Ontario, and during an additional teleconference, held March 29, 2000:

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R. Maronpot, U.S. National Institute of Environmental Health Sciences and National Toxicology Program, and E. Ohanian, Office of Water, U.S. Environmental Protection Agency, provided advice on adequacy of histopathological reporting in one of the critical studies during the teleconference.

The health-related sections of this Report were reviewed and approved by the Health Protection Branch Risk Management meeting of Health Canada

The entire State of the Science Report was reviewed and approved by the Environment Canada/Health Canada CEPA Management Committee.

The text of the Report has been structured to address environmental effects initially, followed by effects on human health.

2.0 SUMMARY OF CRITICAL INFORMATION

2.1 Identity and physical/chemical properties

Ethylene glycol (CAS No. 107-21-1) belongs to the simplest group of organic chemicals of the chemical family of glycols, which are characterized by two hydroxyl (OH) groups at adjacent positions in a hydrocarbon chain (see Figure 1).

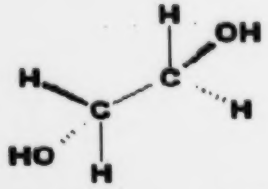


Figure 1. Chemical structure of ethylene glycol

The physicall and chemical properties of ethylene glycol, also known as monoethylene glycol and 1,2-ethanediol, are presented in Table 1. Ethylene glycol is a clear, colourless, odourless, relatively non-volatile, viscous liquid (Nielsen *et al.*, 1993). It has a sweet taste and imparts a warming sensation to the tongue when swallowed (Beasley and Buck, 1980). Ethylene glycol has a relatively low vapour pressure (7–12 Pa at 20°C) (Verschueren, 1983; Howard, 1990) and a low Henry's law constant of 5.8×10^{-6} to 6.0×10^{-3} Pa·m^3/mol (Hine and Mookerjee, 1975; Howard, 1990). It is completely miscible in water (Enviro TIPS, 1985; Budavari *et al.*, 1989). It is very hygroscopic and will absorb up to 200% of its weight in water at 100% relative humidity (Budavari *et al.*, 1989). The octanol/water partition coefficient of ethylene glycol is very low (i.e., log $K_{ow} = -1.36$) (Verschueren, 1983; Budavari *et al.*, 1989; Howard, 1990).

2.2 Entry characterization

2.2.1 Production, importation and uses

Ethylene glycol is produced by three companies located in Alberta: Dow Chemical Canada, located in Fort Saskatchewan; Union Carbide of Canada, Prentiss; and Alberta and Orient Glycol, Prentiss. The Alberta and Orient Glycol plant is the newest of the three and went into operation in September 1994. Shell Canada intends to build an ethylene oxide/glycol plant in Scotford, Alberta, in response to growing worldwide demand (Camford Information Services, 1997). In 1996, the annual production capacity for ethylene glycols (mono-, di- and triethylene glycols) from these plants was 250 kilotonnes from Dow, 300 kilotonnes from Union Carbide and 300 kilotonnes from Alberta and Orient Glycol (Camford Information Services, 1997). This 850-kilotonne production capacity represented an increase from 524 kilotonnes in 1992. The production capacity of the new Shell plant is expected to be 400 kilotonnes per year (Camford Information Services, 1997). The estimated production capacity for 1999 was 907 kilotonnes (Camford Information Services, 1997), with all increases attributable to increased production

by Dow Chemical. The forecasted capacity following operation of the Shell Canada plant will be over 1200 kilotonnes. In 1996, approximately 810 kilotonnes of ethylene glycols (mono-, di- and tri-) were exported from Canada. Import volumes in 1996 were estimated at 31.3 kilotonnes (Camford Information Services, 1997).

In Canada, the majority of ethylene glycol is used in antifreeze formulations (primarily for automotive vehicle engines, but also for aircraft deicing), at 66% (105 kilotonnes) of domestic consumption (Camford Information Services, 1997). According to a survey of Canadian industry carried out under authority of Section 16 of the *Canadian Environmental Protection Act* (CEPA), an estimated 7.7 kilotonnes of ethylene glycol were used in 1996 for aircraft deicing/anti-icing (Environment Canada, 1997b). The amount used for the production of the polyester, polyethylene terephthalate (PETE), in 1996 was relatively small, at 25 kilotonnes (16% of domestic consumption). Natural gas processing used 9.5 kilotonnes (6%) to assist in the removal of water and to prevent ice formation. The remaining 19.5 kilotonnes (12%) was used in the production of solvents, including use as a component in latex paint formulations to guard against paint freezing and as an antifreeze liquid injected into hoses used to pump liquid explosives (Camford Information Services, 1997). The survey of industry carried out under the authority of Section 16 of CEPA for ethylene glycol revealed that in 1995 and 1996, 1.4 kilotonnes and 2.0 kilotonnes were used in the Canadian paints and coatings sector, respectively (Environment Canada, 1997b).

Total worldwide capacity for ethylene glycol is over 10 000 kilotonnes per year, with major increases expected in 2000 and 2001 (Camford Information Services, 1997). Worldwide demand for ethylene glycol stems from the production of fibre and PETE.

In lesser quantities, ethylene glycol may also be used in asphalt emulsion paints; as a coolant and heat transfer fluid; in low-pressure laminates; in brake fluids; in glycol diacetate production; in low-freezing dynamite; as a solvent mixture for cellulose esters and ether; and in cellophane, cosmetics (up to 5%), lacquers, alkyd resins, printing inks, wood stains, leather dyeing, textile processing, humectants, ballpoint pen inks, detergents, solvents, polyurethane foam, medicinals, adhesives and other products (ATSDR, 1993; Lewis, 1993). The quantities used in Canada for each of these products is not known.

2.2.2 Sources and releases

2.2.2.1 Natural sources

Ethylene glycol was identified as one of the substances in the edible fungus *Tricholoma matsutake* (Ahn and Lee, 1986) and has been identified as being a metabolite of the natural plant growth regulator, ethylene (Blomstrom and Beyer, 1980). The relative contribution of ethylene glycol from this or similar sources to levels in the environment is not known, but is expected to be negligible.

2.2.2.2 Anthropogenic sources

2.2.2.2.1 Industrial point sources

According to the National Pollutant Release Inventory (NPRI) database for 1995 and 1996, total industrial releases of ethylene glycol to air, water, underground and land amounted to 4423 and 4167 tonnes for 1995 and 1996, respectively. In Table 2, releases are separated according to environmental compartment.

Releases to air

Of those releases to air, for 1995 and 1996, approximately 76% (420 and 374 tonnes, respectively) can be attributed to the manufacture of ethylene glycol, with essentially 100% of this quantity emanating from a single plant located in Alberta (NPRI, 1995, 1996). A detailed computer simulation of a typical ethylene glycol production plant in Canada producing 270 kilotonnes per year estimated that, on average, 37 tonnes of ethylene glycol would be released to the atmosphere annually if no emission controls were in operation. By contrast, an estimated 1.8 tonnes per year would be released to the atmosphere if appropriate emission controls were implemented (Shen and Minns, 1997). Fugitive releases from equipment leaks are estimated to account for more than 99%, with process vents and wastewater operations contributing very little to ethylene glycol emissions (Shen and Minns, 1997). These predictions are consistent with the low releases reported by two of the three production plants in Alberta.

Other sectors releasing to air include the natural gas sector at 55 tonnes per year (10.5%), based on mass balance analysis, and the paints and coatings industries at 17 tonnes per year (3.5%), for both 1995 and 1996 (NPRI, 1995, 1996). Environmental releases resulting from the use of products from this sector (e.g., paints) are expected to be negligible.

Releases to water

According to NPRI, two industrial sectors are responsible for releasing the majority (91%) of ethylene glycol directly to the aquatic environment. Most releases to water were reported to be from the paper products sector, releasing 37 tonnes (54%) and 44 tonnes (64%) in 1995 and 1996, respectively (NPRI, 1995, 1996). Releases from the paper sector were estimates based on annual purchase volumes, as the ethylene glycol is used primarily as a cooling fluid in closed heat exchange systems. There are some reported practices of applying ethylene glycol directly to the wood chips that are stored outside in the winter months prior to processing. Total volumes released from this practice are not known. All facilities reporting releases in 1996 also indicated use of secondary treatment systems prior to discharge to surface waters (Paper products sector, 1999).

The second most significant source of release to water was identified as the primary steel industry, with release quantities of 25 (37%) and 17 (25%) tonnes per year in 1995 and 1996, respectively (NPRI, 1995, 1996).

It is important to note that although ethylene glycol is used in large volumes for aircraft deicing/anti-icing practices and these volumes are reportedly released to land , airport collection facilities and drainage systems may divert substantial quantities to the aquatic environment (see next section).

Releases to land

Releases to land account for the vast majority of total releases to the environment in Canada, and approximately 95% of these releases originate from activities in the transportation sector — specifically, air transport industries and aircraft servicing industries. Results of tests have indicated that 16% of the glycol used to deice planes remains on the aircraft, 35% is blown behind the aircraft and about 50% falls to the ground in the vicinity of the aircraft following application (North/South Consultants Inc., 1998; Simpson and Kent, 1999). Transport Canada (1996a) indicates that up to 50% of sprayed glycols drain onto the apron surface and subsequently enter drainage runoff or percolate into subsurface soils. In 1995 and 1996, releases from these industries accounted for 3.1 kilotonnes per year, representing more than 75% of the total ethylene glycol released to all environmental compartments each year. It is important to note that although all releases from this sector are reported to be to land, ethylene glycol remains in liquid form, and the deicing collection and drainage facilities may allow large volumes of the ethylene glycol to enter surface water systems. Historically, the runoff from aircraft deicing activities has resulted in the release of large quantities of glycols to the aquatic environment (Transport Canada, 1989a,b,c,d, 1996a).

Deicing of aircraft is a mandatory requirement under regulations provided under the federal *Aeronautics Act*. In the interest of flight safety, these regulations stipulate that aircraft are not permitted to take off with ice on their wings; therefore, airlines, which are responsible for the application of the deicing fluid, often spray large volumes of a heated ethylene glycol-based fluid on aircraft surfaces prior to departure when conditions are conducive to ice formation on the critical surfaces of the aircraft (Transport Canada, 1997a,b, 1998a). At airport facilities, the entry of ethylene glycol into the environment has the potential to be substantial under uncontrolled conditions. Ethylene glycol-based fluid that falls to the ground and is not recovered can find its way into waterways draining airport property via two pathways: meltwater from snow that is contaminated by ethylene glycol and the storm drainage system (North/South Consultants Inc., 1998). Once the aircraft has reached sufficient speed, ethylene glycol "shearoff" from aircraft surfaces may represent another pathway of ethylene glycol entry into the environment (GTAA, 1998).

In 1992, a water quality review at several airports indicated the need to develop and implement glycol operational management plans (GOMPs) to mitigate the effects of aircraft deicing. As a result, GOMPs were subsequently developed by the air carriers and approved by Transport Canada, in accordance with the CEPA Part IV glycol guidelines (Canada Gazette, 1994; Transport Canada, 1997c). Many Canadian airports now have improved means of capturing and/or treating spent aircraft deicing fluids (e.g., through controlled drainage, vacuum collection, diversion to wastewater treatment, etc.) (Transport Canada 1995, 1996a; ATAC, 1999). (For more information on management of ethylene glycol at airports, see Appendix.) As of 1995, the 15 largest airports in Canada had glycol

mitigation plans (GMPs) in place. In combination, these airports use over 90% of all the deicing fluids that are applied to aircraft in Canada (Kent *et al.*, 1999).

Releases underground

The natural gas industries located in Alberta are reported to dispose of the majority of ethylene glycol through on-site underground injection; in 1995 and 1996, this amounted to 564 and 384 tonnes, respectively (NPRI, 1995, 1996). In Alberta, underground injection of waste must receive prior approval from the Alberta Department of Environmental Protection. Guidelines are available, and certain physical requirements must be met to ensure that the waste substance remains underground and that groundwater contamination is avoided. Inspections of the sites are carried out on an annual basis; however, ethylene glycol is not usually measured (Fluorence, 1998). As many of the abandoned natural gas wells are typically several kilometres deep, groundwater contamination can be considered to be negligible.

2.2.2.2.2 Other sources

Total quantities and rates of release of ethylene glycol from use in automotive antifreeze in Canada are not known. Release from this source to the environment can occur through improper disposal during private servicing of motor vehicles and from spillage as a result of vehicle, train or barge accidents (Miller, 1979). An estimated 99 and 88 kilotonnes of ethylene glycol were purchased for use as a component of automotive antifreeze in Canada in 1995 and 1996, respectively (Environment Canada, 1997b).

It is estimated that 25–50% of worldwide use of automobile antifreeze is improperly disposed of (Hudgens and Bustamante, 1993). Experience with highway trucking rigs indicates that they typically lose 10% of coolant volume every 19 000–29 000 km, equivalent to one drop per minute (Hudgens and Bustamante, 1993). A life cycle assessment examining the environmental emissions of ethylene glycol used in automobiles revealed that approximately 0.87 g of ethylene glycol are released to the environment for every litre of antifreeze solution (maximum of 50% ethylene glycol) used during manufacturing, packaging and disposal of the antifreeze (Franklin Associates Ltd., 1994). About 200 g of ethylene glycol are improperly dumped or lost to the aquatic environment for every litre of antifreeze used. It is estimated that approximately 39% of all antifreeze consumed is lost to storm sewers (Franklin Associates Ltd., 1994). Safety Kleen, one of the largest companies in Canada responsible for collecting and recycling used ethylene glycol-based automotive antifreeze, reported acquiring 94 and 88 kilotonnes of used antifreeze, equivalent to 31 and 29 kilotonnes ethylene glycol, in 1995 and 1996, respectively (Environment Canada, 1997b).

Franklin Associates Ltd. (1995) examined the environmental emissions from the life cycle of ethylene glycol-based heat transfer fluids applied to heating, ventilation and air conditioning (HVAC) and to industrial stationary engine cooling systems in the United States and estimated that 2.6, 2.05 and 2.83 g of ethylene glycol are released for every litre of heat transfer fluid used for HVAC, stationary engine cooling fluid and antifreeze, respectively.

In the 20 years between 1974 and 1994, there were 115 environmental spills of ethylene glycol reported to the National Analysis of Trends in Emergency Systems (NATES) database (NATES, 1994). As a percentage of the total spills to the environment, spills to land accounted for 78%, to fresh water, 22%, to air, 2.6%, to groundwater, 2.6%, to seawater, 0.9%, and to sewer systems, 2.6% (total exceeds 100% because some spills involved more than one medium). Although little damage was reported for these spills, some incidents were noted, including three cases of general damage to vegetation and five cases of other non-specified damage. Of all the spills, 22% occurred during transportation, 37% during chemical/petroleum sector operations, 9.6% at government facilities, 8.7% from the mining and metallurgy sectors and 23.5% from other sources. The causes of the spills were reportedly equipment failure (29%), human error (26%) and other causes (44%). The average amount released was 12.9 tonnes per spill, with a maximum of 382.2 tonnes. One reported railway transportation spill resulted in 223 201 L being lost into the North Thompson River in British Columbia. No measurements of ethylene glycol were reported. Surveys of the area by the Fisheries Department reported no fish kills, and the spawning beds remained undisturbed (Christian and Moorehead, 1985).

2.3 Exposure characterization

2.3.1 Environmental fate

2.3.1.1 Air

Based on a measured photooxidation rate constant in air (Atkinson, 1986), the atmospheric half-life for ethylene glycol is estimated to be between 0.35 and 3.5 days (Howard *et al.*, 1991). Ethylene glycol emitted into the atmosphere is subject to photochemical oxidative degradation via hydroxyl radical reactions; because of its high water solubility, it is expected to be washed out of the atmosphere during precipitation events. The estimated atmospheric (tropospheric) lifetime for ethylene glycol is 1.9 days (Bunce, 1996).

2.3.1.2 Water

Biodegradation is the predominant degradation pathway for ethylene glycol in water. Predicted half-lives in water as a direct result of photooxidation-generated hydroxyl radicals are long relative to those of other degradation processes and are estimated to be between 267 days and 64.6 years (Anbar and Neta, 1967; Dorfman and Adams, 1973). Biodegradation occurs much more rapidly in the aquatic environment, with half-lives for surface water estimated to be typically between 2 and 12 days (Howard *et al.*, 1991). Abdelghani *et al.* (1990) determined that ethylene glycol will be significantly degraded by common soil or water microorganisms within the first 3 days of exposure. In a 41-hour study conducted by Gould *et al.* (1989), bacteria isolated from an airport runoff lagoon and from soil samples adjacent to taxiways were able to degrade ethylene glycol up to 100% and 44% at concentrations of 1750 and 7750 mg/L, respectively. It has been cautioned that where releases are significantly large, rapid degradation can result in significant oxygen depletion, with subsequent detriment to the populations of organisms in the receiving water bodies (Sills and Blakeslee, 1992; CCME, 1997a).

The rate of biodegradation depends on numerous factors, including ambient temperature, type and number of microorganisms present, acclimation and the concentration of ethylene glycol in the water body. Temperature is particularly important, as reported by Evans and David (1974), who studied the aerobic degradation of ethylene glycol from grab river water samples at temperatures of 4, 8 and 20°C. At 20°C, ethylene glycol was completely degraded in 3 days in all river waters tested, and at 8°C, degradation was complete within 14 days. Degradation at 4°C was substantially slower, with degradation of less than 20% after 14 days in river samples with limited suspended matter and a starting concentration of 10 mg/L. Similarly, following the protocol for conducting biological oxygen demand (BOD) tests (APHA, 1994), using acclimated soil bacteria and ethylene glycol concentrations of 50 mg/L, biodegradation rate constants were determined to be 0.033, 0.06 and 0.167 per day at temperatures of 4, 10 and 20°C, respectively (Williams, 1995). Corresponding biodegradation half-lives are 21, 12 and 4 days, respectively, assuming a first-order rate of reaction.

Examination of the effect of temperature on the growth of bacterial cultures on minimal medium containing ethylene glycol as the only carbon source revealed that at temperatures of 4, 8 and 14°C, the growth was 6.9, 7.4 and 9.2%, respectively, of that observed in bacteria incubated at 25°C (Graves, 1995). Rate constants for biodegradation of 100 mg ethylene glycol/L by non-acclimatized activated sludge at 20°C were 0.026–0.035 per hour (Urano and Kato, 1986).

All available evidence indicates that ethylene glycol is readily biodegraded aerobically and anaerobically (BUA, 1994; CMA, 1996). Aqueous anaerobic biodegradation half-lives for ethylene glycol have been estimated to fall between 8 and 48 days, based on extrapolations from aqueous aerobic biodegradation data (Howard *et al.*, 1991). Ethylene glycol degradation under anaerobic conditions is dependent on the species of bacteria and has resulted in the formation of ethanol, acetate and possibly acetaldehyde and methane (Dwyer and Tiedje, 1983; Stewart *et al.*, 1995).

At 1440 mg/L in groundwater, ethylene glycol was 94% degraded in 26 days following modification of the groundwater environment through such measures as controlling pH and the introduction of oxygen, nitrogen and phosphorus required to support enhanced bacterial growth (Flathman *et al.*, 1989). Estimates based on surface water degradation rates report groundwater degradation half-lives to range between 4 and 24 days (Howard *et al.*, 1991).

Biodegradation of ethylene glycol using inoculum from groundwater generated rate constants only slightly lower than those found for soils, with a rate constant reported at 0.92 per day ($t_{½}$ = 0.75 days) at 25°C and a concentration of 111 mg/L (McGahey and Bouwer, 1992). It is important to note that ethylene glycol concentration and temperature play important roles in governing the overall degradation rate; in the above study, the temperature of the groundwater was considerably higher than that which would be found under natural conditions in Canada.

2.3.1.3 Soil and sediment

The half-life of ethylene glycol in soil is estimated to be between 2 and 12 days, based on extrapolations from aqueous aerobic biodegradation data (Howard *et al.*, 1991). Although no data were identified for sediment, similar half-lives would be expected in aerobic sediments.

Soil microorganisms are known to biodegrade ethylene glycol. Klecka *et al.* (1993) collected soil from the edge of active runways at airports that used ethylene glycol as a deicing agent. The soil served as a seed for aerobic biodegradation studies, measuring both carbon dioxide production and chemical loss. The authors measured the loss of ethylene glycol in runway soils to be 20–27 mg/kg soil per day at 8°C and 66–93 mg/kg soil per day at 25°C. Soil concentrations of ethylene glycol ranging from 400 to 5000 mg/kg had no inhibitory effect and required no lag phase prior to the onset of degradation.

The rate of biodegradation in simulated subsurface environments was examined by McGahey and Bouwer (1992). Utilizing microorganisms naturally found in soil, the first-order rate constants were found to be between 1.00 and 2.90 per day, and half-lives between 0.69 and 0.24 days, at an ethylene glycol concentration of 100 mg/L and at 25°C. Lowering the temperature from 25°C to 10°C resulted in a decrease in degradation rate by a factor of 2.44, but, in all cases, greater than 99% degradation occurred in less than 7 days (McGahey and Bouwer, 1992). The concentration of ethylene glycol also had a clear effect on degradation. Increasing concentrations of ethylene glycol to 1000 and 10 000 mg/L lowered the rate constant to 0.95 per day ($t_{½}$ = 0.73 days) and 0.05 per day ($t_{½}$ = 13.9 days), respectively.

Ethylene glycol has very low potential for adsorption to soil particles and is thus prone to rapid movement in soil (Hartwell *et al.*, 1993). When releases to soils are large, it is possible that ethylene glycol may not degrade significantly prior to reaching groundwater. Whether ethylene glycol released to soil will result in groundwater contamination is dependent on the degradation and soil permeation rate. Examination of eight different soils indicated that the rate of permeability of ethylene glycol is a function of its dielectric constant. Rates of permeation ranged between 2.31 cm/hour in river bottom sand and 2.43 $\times 10^{-3}$ cm/hour in alfisol (49% clay and 47% silt) (Schramm *et al.*, 1986). In a similar experiment, Løkke (1984) found that movement of ethylene glycol followed closely the movement of water in sandy till soil (17% clay, 78% sand) and meltwater sand (2.6% clay, 90% sand).

2.3.1.4 Environmental partitioning

Based on a Level II fugacity-based environmental equilibrium partitioning model, using input values from Mackay *et al.* (1995) (see Table 1), it is estimated that 99.9% of the ethylene glycol released into the environment will partition into water during steady-state conditions. Output from a fugacity-based Level III steady-state non-equilibrium partitioning model indicated that environmental releases of ethylene glycol will have an overall persistence of 3.2 days, with the majority (96%) of this attributable to reaction, rather than advection. If the aquatic environment is assumed to be the medium of discharge, the Level III fugacity model predicts that 99.97% will remain and react in the water, with 0.03% expected to partition into the sediment porewater. Similarly, a ChemCAN Level III steady-state non-equilibrium fugacity

model depicting a mixed wood plain region of a densely populated area of southern Ontario (Mackay *et al.*, 1996) and using input parameters from Mackay *et al.* (1995) (see Table 1) also predicted overall residence time of 3.2 days, with reaction residence time of 3.3 days, using total releases to air (35 tonnes), water (52 tonnes) and soil (1216 tonnes) in Ontario from NPRI (1996).

The evaporation rate for ethylene glycol was estimated to be 2.97×10^{-8} mol/cm^2 per hour at 20 ± 0.1°C (Gückel *et al.*, 1982). Its relatively low Henry's law constant suggests that it will not evaporate rapidly from either soil or water. Ethylene glycol contains no hydrolysable groups and therefore will not be hydrolysed in the environment and will not directly alter the pH of the water.

Based on its relatively short environmental half-lives and its physical and chemical properties, it is not expected that ethylene glycol will persist or accumulate in soil, sediment or biota.

2.3.2 Environmental concentrations

2.3.2.1 Ambient air

The largest emission of ethylene glycol to the atmosphere reported to the NPRI for 1996 was 374 tonnes per year from ethylene glycol manufacturing plants in Alberta. Using ChemCAN model v.4.0 and attributing all of these releases to one plant, the predicted average background air concentration in the prairie region of Alberta from this emission would be 1.2 ng/m^3. The maximum daily average ground-level ethylene glycol concentrations predicted downwind from the ethylene glycol plant, responsible for approximately 99% of all releases from manufacturing, and using Alberta Environment's SEEC model, were estimated to exceed Alberta's 24-hour ambient guideline of 380 µg/m^3 once per year at a maximum distance of 400 m from the site boundary (Environment Canada, 1997b). Maximum daily average ground-level concentrations were predicted to be 100, 50 and 25 µg/m^3 at distances of 1.8, 4.0 and 6.8 km, respectively, from the property boundary. The annual frequency of occurrence was not reported for these concentrations but is expected to be low based on low frequency of exceedance of Alberta's ambient guideline.

Percy (1992) reported concentrations of ethylene glycol in air of 3.2 and 4.1 mg/m^3 at an Ontario airport. In Louisiana, during bridge deicing operations, total airborne concentrations were between <0.05 and 10.57 mg/m^3; aerosol concentrations were lower (<0.05–0.33 mg/m^3) (Abdelghani *et al.*, 1990). Proximity of measurements to source of release and the time period represented by individual measurements are not known for either of these studies.

2.3.2.2 Indoor air

Data concerning the range and distribution of concentrations of ethylene glycol in non-workplace indoor air in Canada were not identified. Similarly, for the United States, no information about the indoor sources and concentrations of ethylene glycol was identified (CARB, 1997). Concentrations below 0.5 ppm (i.e., 1270 µg/m^3) cannot be detected by currently available sampling and analytical methods for the determination of ethylene glycol in ambient, indoor and workplace air (ATSDR, 1997).

2.3.2.3 Drinking water

Data concerning concentrations of ethylene glycol in drinking water in Canada were not identified. Similarly, no information was identified concerning the range and distribution of concentrations of ethylene glycol in drinking water in the United States (ASTDR, 1997) or elsewhere. Analytical methods used for the determination of ethylene glycol in surface water and groundwater are generally limited to concentrations greater than 1–10 mg/L, as indicated below.

2.3.2.4 Surface water and groundwater

Data on concentrations of ethylene glycol in surface water in Canada are limited to samples taken in the vicinity of airports. Data on ambient levels are limited. Truro Creek, a small tributary to the Assiniboine River, flowing through Winnipeg International Airport property, was reported to have concentrations of glycols measured in the spring of 1996 ranging from 2 to 660 mg/L (75% frequency of detection; n = 12) (North/South Consultants Inc., 1998). Concentrations of ethylene glycol were below 10 mg/L (n = 19) in the spring of 1997. Thirty-nine samples were collected at this same location in the spring of 1998 (March 18 – June 3), with concentrations ranging from largely undetected (8% frequency of detection) to 83 mg/L (North/South Consultants Inc., 1998). Concentrations were not detectable approximately 2 km downstream of this sampler.

Measurements of ethylene glycol in Etobicoke Creek, which receives stormwater effluent from Lester B. Pearson International Airport in Toronto, were less than the detection limit (<25 mg/L) in October 1996 and March 1997. The samples were taken from four stations, from property line to 1 km downstream from the effluent outfall (Beak International Inc., 1997). Water temperatures were between 10 and 11°C, and dissolved oxygen (DO) levels were 11 mg/L for four downstream locations in October; similarly, in March, temperatures were between 3 and 5°C, and DO levels were 12.7 mg/L (Beak International Inc., 1997).

Ethylene glycol concentrations have also been routinely measured in Outer Cove Brook, which runs through the property of the St. John's International Airport in Newfoundland and is known to be the habitat for a variety of fish. Seventeen measurements recorded in the 1997/98 season revealed concentrations in the brook to fall between 5 mg/L (detection limit) and 80 mg/L, with a median of 5 mg/L. Concentrations (n = 140) in the following season, 1998/99, ranged from 5 mg/L (detection limit) to 170 mg/L, with a median of 12 mg/L (Roach, 1999).

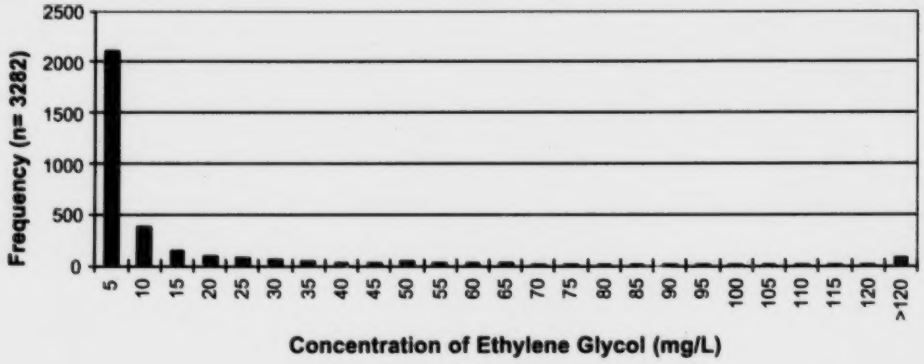
Historically, high levels of ethylene glycol have been reported in stormwater at a number of airports in Canada (Transport Canada, 1995, 1996a, 1989a,b,c,d). Total glycol levels in the effluents from Canadian airports have been monitored for almost 10 years and on a regular basis since 1994 as part of GMPs and GOMPs in cooperation with Transport Canada, the Air Transport Association of Canada (ATAC) and individual airport authorities. This has encouraged the initiation of remediation and environmentally protective management activities (Transport Canada, 1995, 1996b, 1997a; ATAC, 1999).

Table 3 presents a summary of recent ethylene glycol measurements for stormwater effluent from 32 of Canada's larger airports, which account for over 95% of the ethylene glycol used in Canada for aircraft deicing (ATAC, 1999; Leroux, 1999). In order to ensure that data presented in the table reflect concentrations reaching the natural environment, sampling stations located in the direct vicinity of deicing operations or that monitor containment ponds have not been included. Emphasis has been placed on sampling stations that are located at the airport property boundary or that monitor effluents leading directly to a drainage ditch or watercourse near airport property. Only data from the two most recent deicing seasons, 1997/98 and 1998/99, are presented. Both grab and composite samples are in this summary, and all individual measurements were weighted equally.

For individual airports over both the 1997/98 and 1998/99 seasons, mean concentrations of ethylene glycol ranged from below the detection limit (1–10 mg/L) to 411 mg/L (Sudbury Airport, 1997/98). High mean values were also recorded for Prince George Airport (196 mg/L) in the 1998/99 season, as well as Gander International Airport in the 1998/99 season (95 mg/L). Median values are much less than the means and ranged from below detection for the majority of airports to 50 mg/L for the Saint John New Brunswick Airport in the 1998/99 season; however, considering the size of this particular data set (n = 5), the significance of this statistic is questionable. Other airports having relatively high median values are Sudbury (39 mg/L) in the 1997/98 season and Gander International (25 mg/L) in the 1998/99 season. While the vast majority of airports have maxima under 400 mg/L, a few airports recorded maxima over 3000 mg/L, such as Québec Jean Lesage International Airport (4700 mg/L) in March 1999 and Montreal Dorval (3700 mg/L) in January 1998, attributed to the "ice storm" of 1998.

Figure 2 illustrates the distribution of 3282 individual measurements of ethylene glycol sampled in stormwater at airports across Canada over both the 1997/98 and 1998/99 deicing seasons. Key percentiles in this distribution and the breakdown by season are summarized in Table 4. Generally, mean glycol concentrations measured over these 2 years were similar, but substantially reduced from those of the 1996/97 season. The higher concentrations of glycol in stormwater in the 1996/97 season were largely due to releases at Dorval International Airport. However, a $35 million glycol management infrastructure was put in place in November 1997 (AXOR, 1999), effectively reducing glycol exceedances in recent years. A few maxima tend to be very high in relation to the entire data set of recent years (e.g., 4700 mg/L measured at Québec Jean Lesage International Airport in March 1999). The large drop in concentration of the 99th percentile (200 mg/L) from the maximum value of 4700 mg/L illustrates that such very large values are exceptional. See Appendix for further information on management of deicing/anti-icing fluids at Canadian airports.

Figure 2. Distribution of concentrations of ethylene glycol (mg/L) in stormwater of Canadian airports over two deicing seasons (1997/98 and 1998/99)



Data on groundwater concentrations of ethylene glycol are very limited, but some measurements have been taken at Calgary International, Charlottetown, Montreal International (Dorval and Mirabel) and Ottawa Macdonald-Cartier International airports. These data are summarized in Table 5. Some exceptionally elevated values greater than 10 000 mg/L have been reported at Calgary International Airport, with a maximum of 46 769 mg/L recorded in May 1997. However, this high value, along with seven other values greater than 10 000 mg/L, are limited to samples taken from groundwater holes located under the apron where almost all of the commercial aircraft activity takes place. Furthermore, these samples were taken at a very shallow depth (generally under 1 m) under deicing areas. Combined with a clay till soil composition and very slow migration, such high concentrations of ethylene glycol would be expected. Contamination appears to be localized, as samples taken from other locations and aprons on Calgary airport property generally had non-detectable or low concentrations, with a mean of 4 mg/L and a maximum of 38 mg/L (as summarized in Table 5). Such results are in agreement with 1997/98 groundwater data from the Charlottetown and Montreal airports, which ranged from non-detectable to a maximum of 42 mg/L (Aéroports de Montréal, 1999; Transport Canada, 1999d), with over 84% of samples having glycol concentrations less than 10 mg/L.

Groundwater concentrations of ethylene glycol were measured several years ago at Ottawa International Airport (Macdonald-Cartier), where susceptibility to groundwater contamination is high due to permeable soils and the presence of an unconfined aquifer. Samples collected from wells located adjacent to the runways between 1985 and 1986 were generally below the detection limit (5 mg/L); however, one elevated level was measured in June 1986 at 415 mg/L, at a distance of approximately 600 m from terminal. The only other samples with levels above the detection limit were also collected on the same date, at 14 and 20 mg/L in two other wells (Transport Canada, 1987). Ethylene glycol was also present in groundwater samples taken in December 1985 and January 1986 at levels of 22 and 24 mg/L, respectively (Transport Canada, 1987). Using a computer model to estimate down-gradient concentrations over 20 years of cyclic loading, it was demonstrated that concentrations in groundwater can be expected to decrease, with the relative concentration of glycol varying from 0 to 0.3 times the source concentrations. Long-term increases in glycol concentrations were not measured at any of the

monitoring stations at the Ottawa airport, and rapid degradation of the glycol in the groundwater seems to occur.

Contamination of snow, particularly along airport runways, has received very limited investigation. In some preliminary studies, the Greater Toronto Airport Authority measured the concentration of glycols in snow at three sites at various distances from the runway where glycol was expected to be found (GTAA, 1998). Sampling occurred after a major winter storm event, during which a total of 528 385 L of aircraft deicing fluids were sprayed on 786 aircraft. The concentration of ethylene glycol in snow ranged from 98 to 521 mg/L. In addition, one site 750 m away from the edge of the runway, selected to represent the environmental background concentration for glycol in snow in the vicinity of the airport, had a concentration of 22 mg/L. In a groundwater assessment report by Transport Canada, source concentrations of glycol in the snow adjacent to airport taxiways were measured as high as 7300 mg/L (Transport Canada, 1985). These preliminary results indicate that glycol "shearoff" from the aircraft during takeoff may represent an important pathway for glycol to reach the environment (GTAA, 1998).

As noted above (see Section 2.2.2.2), the air transportation industry is not the only sector responsible for releasing quantities of ethylene glycol to water. According to NPRI for 1995 and 1996, steel industries are also responsible for releases of ethylene glycol to the aquatic environment. Effluent concentrations from a steel manufacturing operation, which was responsible for the highest releases from this sector (11 tonnes, or 64% of the total volume released to water from the steel industry in 1996; NPRI, 1996), were estimated to be less than 1 mg/L before any natural biodegradation from their treatment facilities (Saldanha, 1999). Concentrations in the wastewater from the second largest releaser from this sector are also expected to be minimal, as all wastewater from this facility undergoes at least primary treatment. The third steel manufacturing facility was reported to release ethylene glycol in wastewater discharge at concentrations below the detection limit (5 mg/L) for 1995 and 1996 (Environment Canada, 1997b). At the present time, ethylene glycol-based hydraulic fluid at this facility has been replaced by a non-ethylene-glycol-based fluid (Bortnick, 1999).

Wastewater from an ethylene glycol production facility in June 1997 contained ethylene glycol at <2 mg/L in an effluent stream flowing directly into an adjacent river (Environment Canada, 1997b).

2.3.2.5 Sediment, soil and biota

Measurements of ethylene glycol in soils in Canada are very limited, and measurements in sediment or biota are not available. NPRI (1995) reported that the largest releases by volume of ethylene glycol in Canada were to land, but, as noted previously, most of these releases are from airport deicing/anti-icing operations and are expected to enter local surface water and groundwater. An analysis of soil surface porewater samples collected in September 1998 from Sudbury Airport, at the location where ethylene glycol-contaminated snow is piled, revealed all concentrations below the detection limit (4 mg/L) (Transport Canada, 1998b). In Louisiana, ethylene glycol was not detected in soil and sediments (detection limit <1.0 mg/L) from samples collected below state bridges immediately following deicing operations (Abdelghani *et al.*, 1990).

Ethylene glycol was detected in 2 of 73 soil samples collected in 1994 around an ethylene glycol manufacturing plant in Alberta. The concentrations in these two samples were 119 and 4290 mg/kg, and the limit of detection was 5 mg/kg (AEP, 1996).

2.3.2.6 Food

Data concerning concentrations of ethylene glycol in foods in Canada were not identified. Elsewhere, the presence of ethylene glycol has been demonstrated in only a very small number of food items. In Italy, ethylene glycol was detected in all 44 samples of wine analysed by gas chromatography–mass spectrometry. The average and maximum concentrations were 2.8 and 6.25 mg/L, respectively (Gaetano and Matta, 1987). However, the source of ethylene glycol in wines is not known (Gaetano and Matta, 1987; Kaiser and Rieder, 1987). In Japan, ethylene glycol was present in the headspace volatiles of roasted sesame seeds, but quantitative data were not provided (Takei, 1988).

Foods that have been disinfected or preserved with ethylene oxide may contain residual ethylene glycol. In France, Buquet and Manchon (1970) sampled 150 bread loaves preserved with carbonic anhydride and ethylene oxide and packaged in air-tight plastic bags. The initial concentrations of ethylene glycol ranged from not detected (detection limit not reported) to 92.2 ppm (mg/kg) but quickly subsided. In Canada, ethylene oxide is not, nor has it ever been, permitted for use in bread (Salminen, 2000). However, in Canada, there is a provision under the Food and Drugs Regulations for the use of ethylene oxide to fumigate spices. Available data show that residues from such use, under normal conditions, are negligible (Salminen, 2000). In France, Chaigneau and Muraz (1993) sampled 16 spices that had been disinfected using ethylene oxide. Concentrations of ethylene glycol were not reported, and the authors indicated that residual ethylene glycol was rapidly lost.

The potential for ethylene glycol to migrate into beverages contained in PETE bottles and into foods packaged in regenerated cellulose film (RCF) has been demonstrated, resulting from small amounts of unreacted ethylene glycol in such products (Kashtock and Breder, 1980; Castle *et al.*, 1988; Kim *et al.*, 1990). Kashtock and Breder (1980) measured the migration of ethylene glycol at 32°C from PETE bottles into 3% acetic acid (intended to simulate carbonated beverages). Time-dependent increases in average concentrations were measured, resulting in a maximum concentration of 104 µg/L after 6 months' storage at this elevated temperature.

RCF is widely used as a food packaging material, since its permeability, sealability and ease of application for twist wrapping are desirable for packing certain foods. In the United Kingdom, Castle *et al.* (1988) measured the ethylene glycol content of several foodstuffs wrapped in RCF at random intervals up to the end of their usual maximum shelf-lives. Four samples of boiled sweets contained ethylene glycol at concentrations ranging from 14 to 34 mg/kg. Three of four samples of toffee contained ethylene glycol, with a maximum concentration of 22 mg/kg. Two of four samples of Madeira cake contained ethylene glycol, with a maximum concentration of 22 mg/kg. All four samples of fruit cake contained ethylene glycol, with a maximum concentration of 34 mg/kg. Ethylene glycol was not detected in any of the six samples of meat pie, with a limit of detection of 10 mg/kg.

2.3.2.7 Consumer products

Several products used in the operation or maintenance of automobiles typically contain ethylene glycol. Concentrations ranging up to 85% may have been present in older automotive brake fluids (U.S. EPA, 1986); however, the ethylene glycol content of current brake fluids is less than 0.1% (ATSDR, 1997). Antifreeze solutions in automobile coolant systems typically have an ethylene glycol content of 50% (Franklin Associates Ltd., 1995). Windshield washer fluids intended for use during winter may contain ethylene glycol at up to 14% by weight (Flick, 1986, 1989). The ethylene glycol content of automobile wax and polish can range up to 3% by weight (U.S. EPA, 1986).

Ethylene glycol may also be present in wax and polish intended for use in the home. Flick (1986) reported concentrations ranging from 1.1% to 1.4% in four types of floor polish. Concentrations ranging up to 3.5% may be present in floor wax and polishes, according to U.S. EPA (1986).

Ethylene glycol may be present as a slow-evaporating solvent and/or freeze-thaw stabilizer in latex paints (U.S. EPA, 1986). Chang *et al.* (1997) estimated that latex paints comprised over 85% of the interior coatings used in the United States in 1992 and reported concentrations of ethylene glycol ranging from 23.3 to 25.8 mg/g (from 2.3% to 2.6% by weight) in four samples of medium-priced paints. Eleven Canadian paint and coatings companies reported that their products may contain up to 5% of ethylene glycol by weight (Environment Canada, 1997b).

Other consumer products that may contain ethylene glycol include tub and tile cleaners (3% by weight) and cement sealer (2.2% by weight) (Flick, 1986).

Ophthalmic solutions (eye drops) that have been treated with ethylene oxide as a sterilant may contain ethylene glycol and ethylene chlorohydrin as residues. In the United States, Manius (1979) detected ethylene glycol in 4 of 15 samples of ophthalmic solution, with a range of 10–28 mg/L (detection limit of 6 mg/L). However, in Canada, the use of ethylene oxide as a sterilant of non-prescription eye drops is not expected (Lapner, 2000).

The only cosmetic registered for use in Canada that lists ethylene glycol as an ingredient is a solid stick foundation, distributed from Quebec. The concentration of this ingredient was not available (Denman, 1999).

2.4 Effects characterization

2.4.1 Ecotoxicology

This toxicity section focuses exclusively on the effects of pure ethylene glycol, although it is understood that ethylene glycol-contaminated fluids (e.g., formulated aircraft deicing fluid) released to the environment often include other substances. It is also understood that in the majority of cases, except for a few species of plants, deicing fluids have been found to be several times more toxic than pure ethylene

glycol alone (Jank *et al.*, 1973; Aéroports de Montréal and Analex Inc., 1994; Ward, 1994; Fisher *et al.*, 1995; Hartwell *et al.*, 1995; Pillard, 1995; Cancilla *et al.*, 1997; Union Carbide, 1997a, 1999; Kent *et al.*, 1999; Pillard and Dufresne, 1999).

2.4.1.1 Direct effects

2.4.1.1.1 Microorganisms

Based on limited data, terrestrial microorganisms appear to be less sensitive to ethylene glycol than aquatic microorganisms. Terrestrial microorganisms have demonstrated adverse effects at concentrations ranging from 2000 to 200 000 mg/L. An average concentration causing a 50% reduction in growth (IC_{50}) for heterotrophic soil microorganisms has been reported to be 114 300 mg/L (Khoury *et al.*, 1990). In the only identified study on the chronic toxicity of ethylene glycol to aquatic protozoa, Beak Consultants Ltd. (1995a) reported a 24-hour EC_{50} of 28 090 mg/L for growth inhibition in the ciliated protozoan, *Colpidium campylum*.

2.4.1.1.2 Plants

Adverse effects have been reported for both aquatic and terrestrial plants exposed to ethylene glycol. The green alga, *Selenastrum capricornutum*, is identified as the most sensitive aquatic species to ethylene glycol. The effect of ethylene glycol on the growth of this algal species has been examined by several authors (Dill *et al.*, 1982; Ward *et al.*, 1992; Aéroports de Montréal and Analex Inc., 1994; Beak Consultants Ltd., 1995b; Pillard and Dufresne, 1999). All of the tests followed essentially the same test method (U.S. EPA, 1978, 1989a,b) and measured the same cell growth endpoint. Where possible, IC_{25}s were determined, using parametric and/or non-parametric analysis. The study by Aéroports de Montréal and Analex Inc. (1994) reported the lowest IC_{25}s, ranging from 592 to 4479 mg/L from three experimental trials and derived using non-parametric analysis, with a mean of 3268 mg/L. The highest IC_{25} was 8825 mg/L based on nominal concentrations using a non-parametric linear interpolation method (Beak Consultants Ltd., 1995b). In the other studies, Dill *et al.* (1982) observed growth inhibition of over 80% after 96 hours at the highest concentration (22 300 mg/L), which was reduced to 30% inhibition after 7 days. This reduction in inhibition is supported by the work done by Ward *et al.* (1992), who reported 48-, 72-, 96- and 336-hour (2-, 3-, 4- and 14-day) EC_{50} values for population growth of 13 100, <6400, 7900 and 18 200 mg/L, respectively. There was no explanation for the increased EC_{50} after 336 hours compared with the shorter exposures. In the same study, growth at 27 000 mg/L after 96 hours was 14% of the control and after 14 days had risen to 42% of the control value. The reduction in inhibition was not due to a change in ethylene glycol concentrations over time, as the final measured concentrations were 90% of the initial values.

For another algal species, *Scenedesmus quadricauda*, and a cyanobacterium, *Microcystis aeruginosa*, an 8-day EC_3 (threshold inhibition) was >10 000 mg/L and 2000 mg/L, respectively, as reported by Bringmann and Kuhn (1978). Ward and Boeri (1993) examined the effect of ethylene glycol on the alga, *Chilomonas paramecium*, following a 48-hour (population growth) study, where the EC_{50}

was 53 200 mg/L. Pillard and Dufresne (1999) determined the 96-hour IC_{25} and IC_{50} for frond growth in duckweed, *Lemna minor*, to be 17 120 mg/L and 47 750 mg/L, respectively.

Data on effects of ethylene glycol on terrestrial plants are limited. Pillard and Dufresne (1999) exposed lettuce (*Lactuca sativa*) and rye grass (*Lolium perenne*) seedlings to solutions of ethylene glycol between 1200 and 150 000 mg/L and determined the 120-hour IC_{25} for emergence, root length and shoot length to be 21 750, 25 100 and 8960 mg/L for lettuce and 19 700, 3620 and 5100 mg/L for rye grass, respectively. Similarly, the 120-hour IC_{50}s for the same measurement endpoints, respectively, were 60 000, 34 030 and 26 530 mg/L for lettuce seedlings and 28 440, 22 450 and 11 730 mg/L for rye grass seedlings (Pillard and Dufresne, 1999). In a similar test, radish (*Raphanus sativa*) and lettuce exposed to ethylene glycol in nutrient solutions had EC_{25}s for root elongation of 17 000 and 32 000 mg/L, respectively (Environment Canada, 1994). In this same study, seedling emergence in artificial soil resulted in an EC_{25} of 5300 mg/kg soil (72 hours) and 9000 mg/kg soil (120 hours) for radish and lettuce, respectively.

2.4.1.1.3 Invertebrates

Acute

The available data on freshwater toxicity indicate that aquatic invertebrates are slightly more sensitive to ethylene glycol than fish (see Section 2.4.1.1.4). Aquatic invertebrate acute LC_{50} values range from 10 000 mg/L for *Ceriodaphnia dubia* for a 48-hour exposure (Cowgill *et al.*, 1985) (note: control group loss in this study was greater than 10%) to 91 430 mg/L for crayfish, *Procambarus* sp., for a 96-hour exposure (Abdelghani *et al.*, 1990). A 48-hour EC_{50} (immobilization) of 50 450 mg/L was reported for *Daphnia magna* (Hermens *et al.*, 1984). Pillard (1995) exposed *C. dubia* to ethylene glycol for 48 hours and reported an LC_{50} of 34 440 mg/L and a No-Observed-Effect Concentration (NOEC) of 24 000 mg/L.

Only one study on the toxicity of ethylene glycol to terrestrial invertebrates was identified. The earthworm, *Eisenia foetida*, was exposed to ethylene glycol in an artificial soil. The 14-day LC_{25} was reported as 20 000 mg/kg soil based on nominal concentrations (Environment Canada, 1994).

Chronic

In two recent chronic studies, the effects of ethylene glycol on reproduction and survival of *Ceriodaphnia dubia* have been examined (Beak Consultants Ltd., 1995a; Pillard, 1995). The duration of both studies was 7 days, during which time three broods were produced. Beak Consultants Ltd. (1995a) reported 7-day NOEC and Lowest-Observed-Effect Concentration (LOEC) values to be 25 957 and 53 950 mg/L for survival and 3469 and 6716 mg/L for impaired reproduction, respectively. The 7-day EC_{25} and EC_{50} values for impaired reproduction were 9226 and 16 315 mg/L, respectively (Beak Consultants Ltd., 1995a). Pillard (1995) conducted a similar short-term chronic study using *C. dubia* (test duration equal to the time required for three broods from 60% of control population) and reported NOEC values of 8590 and 24 000 mg/L for reproduction and mortality, respectively, as well

as an EC_{25} of 12 310 mg/L for reduced reproduction. The effects of ethylene glycol on reproduction in the rotifer, *Brachionus calciforis*, were recently assessed by Beak Consultants Ltd. (1995c). The 48-hour NOEC, LOEC and EC_{50} values were 12 800, 23 600 and 26 461 mg/L, respectively.

2.4.1.1.4 Fish

Acute

In acute toxicity studies on fish, 96-hour LC_{50} values have ranged from 17 800 mg/L for rainbow trout (*Oncorhynchus mykiss*) to >111 000 mg/L for bluegill sunfish (*Lepomis macrochirus*) (Mayer and Ellersieck, 1986). Beak Consultants Ltd. (1995a) conducted acute exposure studies with rainbow trout; 96-hour LC_{50} values were 22 810 and 24 591 mg/L for duplicate trials. Könemann (1981) reported a 168-hour LC_{50} of 49 300 mg/L for the guppy (*Poecilia reticulata*). Ward *et al.* (1992) reported 24-, 48-, 72- and 96-hour LC_{50}s ranging from 50 400 to 83 400 mg/L for fathead minnows (*Pimephales promelas*) and from 50 800 to 65 100 mg/L for rainbow trout. Ward *et al.* (1992) also reported 24- to 96-hour LC_{50}s for a marine fish, sheepshead minnow (*Cyprinodon variegatus*), ranging from 27 600 to 81 700 mg/L. Pillard (1995) exposed fathead minnows to ethylene glycol and reported 48- and 96-hour LC_{50}s of 81 950 and 72 860 mg/L, respectively. The 96-hour NOEC for mortality was 39 140 mg/L. The histological effects of acute exposure of fathead minnows to ethylene glycol were reported by Hartwell *et al.* (1995). Histological changes apparent after exposure to 70 mL/L (78 000 mg ethylene glycol/L) included respiratory cell necrosis, intralamellar edema and disruption of the respiratory epithelium.

Although the metabolic link between oxalate crystal formation and ethylene glycol is clear in mammals (Carney, 1994; see also Sections 2.4.1.1.6, 2.4.3.3 and 2.4.3.4), the link between oxalate crystal formation and adverse effects on aquatic populations is not as apparent. Hartwell *et al.* (1995) exposed fathead minnows to concentrations of ethylene glycol-based deicing fluids in use at Baltimore Washington International Airport and examined surviving fish histologically. Acute exposure to ethylene glycol-based deicing fluids resulted in a constant 48-hour, 96-hour and 7-day LC_{50} of 9.82 mL ethylene glycol/L (10 900 mg/L) (95% confidence interval = 8.30–11.63 mL/L). The main histological response of fathead minnows exposed to high concentrations (70 mL/L [78 000 mg/L]) of glycol-based deicer fluid was seen in the gills, where respiratory cell necrosis, intralamellar edema and disruption of the respiratory epithelium occurred. Renal lesions occurred at lower concentrations, as acute tubular necrosis and the appearance of oxalate crystals. After 24 hours of exposure to the deicing fluid, oxalate crystals were observed only at 4875 mg ethylene glycol/L, although moderate lesions were observed at concentrations between 4875 and 78 000 mg/L, and the severity was not concentration dependent. Between 4 and 7 days, oxalate crystal formation was observed at all concentrations of ethylene glycol between 1114 and 9740 mg/L, although, again, severity of lesions was not concentration dependent. Similarly, Evans (1990) reported kidney damage in tessellated darters (*Etheostoma olmstedi*) and American eels (*Anguilla rostrata*) found in the creek adjacent to the airport 1 month after deicing had stopped. In the same study, kidney lesions consistent with oxalate crystal damage were observed, although oxalate crystals were not observed. It is important to note that the results of the Hartwell *et al.* (1995) and Evans (1990) studies are difficult to interpret due to the presence of the formulated product

rather than ethylene glycol alone. In addition, Hartwell *et al.* (1995) did not establish a concentration–response relationship, making interpretation of cause and effect difficult. As well, the effects were essentially histological and may not result in significant population-level effects.

Subchronic/chronic

The chronic toxicity data for early life stages of both rainbow trout and fathead minnows suggest that freshwater fish are affected by chronic or long-term ethylene glycol exposures. Beak Consultants Ltd. (1995a) exposed rainbow trout from the late sac fry stage to 5 days post-swim-up (12 days). The NOECs for both growth and mortality were reported to be 14 692 mg/L. The next highest exposure concentration of 28 333 mg/L was reported as the LOEC for both growth and mortality; however, it should be noted that this treatment resulted in 100% mortality. Two 7-day chronic toxicity tests using fathead minnows were recently completed (Beak Consultants Ltd., 1995a; Pillard, 1995). Both Beak Consultants Ltd. (1995a) and Pillard (1995) found growth to be a more sensitive indicator of chronic toxicity than mortality. Beak Consultants Ltd. (1995a) reported fathead minnow 7-day NOEC, LOEC, IC_{25} and IC_{50} values for growth of 12 531, 24 569, 24 806 and 37 318 mg/L, respectively. When mortality was used as the experimental endpoint, the 7-day NOEC, LOEC and LC_{50} values were 24 569, 51 886 and 47 332 mg/L. Note that the LOEC exceeds the LC_{50}, indicating that intra-treatment variability was high and/or that treatments were applied at inappropriate concentration intervals. Pillard (1995) found a 7-day NOEC and EC_{25} for the growth of fathead minnows to be 15 380 and 22 520 mg/L, while the 7-day NOEC for mortality was 32 000 mg/L.

2.4.1.1.5 Amphibians

The limited toxicity data on clawed toads (*Xenopus laevis*) suggest that the sensitivity of amphibians to ethylene glycol is likely similar to or higher than that of freshwater fish. Beak Consultants Ltd. (1995a) used an ASTM (1994) protocol to expose 3- to 4-week-old clawed toads to ethylene glycol and reported 48-hour LC_{50}s of 19 350 and 15 667 mg/L in duplicate trials.

2.4.1.1.6 Mammals and birds

Ethylene glycol imparts a sweet or semi-sweet taste to fluids such as antifreeze, which encourages animals to consume it (Amstrup *et al.*, 1989). Ethylene glycol poisoning is common among domestic animals and has been reported in cats, pigs, poultry, wildlife and calves (Kersting and Nielsen, 1965; Riddell *et al.*, 1967; Black, 1983; Amstrup *et al.*, 1989). Ethylene glycol is a slow-acting poison. Even after a massive dose, an animal will be unaffected for 0.5–2 hours post-exposure (Lakshmipaty and Oehme, 1975; Oehme, 1983; Beasley, 1985; Grauer and Thrall, 1986). The toxicity of ethylene glycol varies among species. Cats were reported to be the most susceptible to poisoning (Osweiler *et al.*, 1985). The reported lethal dose for cats is only 1.5 mL/kg-bw (1650 mg/kg-bw) (Black, 1983), whereas for dogs it is 4.2–6.6 mL/kg-bw (4620–6600 mg/kg-bw) (Beasley and Buck, 1980; Oehme, 1983; Grauer and Thrall, 1986). Osweiler *et al.* (1985) reported a lethal dose of 2–4 mL/kg-bw (2200–

4400 mg/kg-bw) in cats, 4–5 mL/kg-bw (4400–5500 mg/kg-bw) in dogs and 7–8 mL/kg-bw (7700–8800 mg/kg-bw) in poultry. Mallard ducks (*Anas platyrhynchos*) exposed orally to ethylene glycol demonstrated adverse toxic effects (Lowest-Observed-Effect Dose, or LOED) at 2.3 mL/kg-bw (2530 mg/kg-bw) (Stowe *et al.*, 1981).

Symptoms of ethylene glycol poisoning in birds and mammals include general weakness, depression, vomiting and loss of muscular coordination. Ingestion of large doses may cause severe depression, metabolic acidosis, coma, cardiopulmonary collapse and death. Formation of oxalate crystals and lesions in kidneys due to ethylene glycol poisoning has been reported in swine, cattle, sheep, cats, dogs and poultry (Riddell *et al.*, 1967; Osweiler and Eness, 1972; Crowell *et al.*, 1979; Beasley, 1985; Osweiler *et al.*, 1985; Boermans *et al.*, 1988).

Ren *et al.* (1996) reported that ethylene glycol has a weak estrogenic effect on rainbow trout (*Oncorynchus mykiss*); however, estrogen and androgen binding affinity of ethylene glycol analysed through computer modelling was reported to negative for estrogen and androgen receptors (Mekenyan, 1999, unpublished) and. In addition, a sensitive bioassay examining the binding affinity for estrogen receptors showed that ethylene glycol had no activity from 10^{-8} to 10^{-4} M (Prechtl, 1999, unpublished). From these additional experiments, it is apparent that any estrogen activity from the Ren et al., 1996 paper could be the result of contamination from the leaching of active chemicals from certain plastic materials or through atmospheric contamination by active chemicals (Soto A., pers. comm. 1999).

2.4.1.2 Indirect effects

As a result of biodegradation, the release of ethylene glycol into surface waters such as small rivers and streams has the potential to lower the DO level (see also Section 2.3.1.2). If the conditions for bacterial growth are satisfactory and there is enough ethylene glycol, then the levels of oxygen could drop below that which is necessary to maintain the productivity of the water body. Ethylene glycol has a theoretical oxygen demand of 1.29 mg O_2/mg, indicating that 2.5 mol of oxygen are required to break down each mole of ethylene glycol. There have been some reported cases of a depletion of DO associated with the release of ethylene glycol-based deicing and/or anti-icing fluids in water systems near airports (Schulz and Comerton, 1974; Transport Canada, 1989a,b,c,d; Sills and Blakeslee, 1992; Fisher *et al.*, 1995), and the association is recognized by the major ethylene glycol-based deicing fluid supplier (Union Carbide, 1997a,b, 1999).

The BOD is a test used to measure the DO consumed by aquatic microbial life while assimilating and oxidizing the organic matter present in the dark and usually at 20°C for 5 days. It is a parameter that is commonly measured for effluent discharge at Canadian airports and can be quite high as a direct result of the presence of ethylene glycol (Transport Canada, 1989a,b,c,d; Union Carbide, 1997a,b, 1999). In Canada, there exists a BOD_5 (5 day) effluent guideline of 20 mg O_2/L, which is a voluntary limit that applies to all existing or proposed land-based federal establishments discharging to surface waters (Environment Canada, 1976c). Use of this guideline is intended to promote both a consistent approach towards the cleanup and prevention of water pollution and the use of the best available control

technology in Canada (Environment Canada, 1976c). The guideline is based on technical limitations of water treatment systems and so is not effects based (Haskill, 1999).

The relationship between BOD and ethylene glycol concentrations in aircraft deicing fluids has been examined on a number of occasions. Because the BOD of stormwater from the Halifax International Airport was observed to be quite high in 1989 and 1990 (Transport Canada, 1990), an experiment was conducted to examine this relationship. Transport Canada (1990) correlated the BOD and ethylene glycol (EG) concentrations using linear regression analysis (n = 25, $r^2 = 0.962$) and derived the following equation (Transport Canada, 1990):

$$[EG mg/L] = (BOD \times 2.49) - 396.28$$

Similarly, Schulz and Comerton (1974), using regression analysis, determined that the relationship between BOD and ethylene glycol (mg/L) in stormwater runoff was:

$$[EG mg/L] = \frac{BOD + 50}{0.85}$$

Sills and Blakeslee (1992) determined that ethylene glycol at 11 140 mg/L in stormwater runoff equates to a BOD_5 of 5000 mg O_2/L. It is apparent that although attempts to establish a mathematical relationship between BOD and ethylene glycol are not always consistent, the high oxygen demand from ethylene glycol is evident. Any differences in the derived equations may be due to formulation deicing fluid versus pure ethylene glycol, experimental versus field conditions, or the time of sampling for ethylene glycol versus time of sampling for BOD at any given location. It is evident from these analyses that the theoretical oxygen demand from ethylene glycol may be a conservative estimate of the actual BOD from effluent releases.

Natural DO levels in Canadian waters have been observed to range from non-detectable to above saturation (see also Section 3.1.2.2). Low oxygen levels may cause a variety of effects, including lethal and sublethal effects (reduced growth, loss of equilibrium, reduced or increased opercular movement, surface respiration, reduced activity and avoidance behaviour), in various aquatic organisms, with younger fish being notably more sensitive than older fish (CCME, 1999). Salmonids are among the most sensitive fish species (Davis, 1975; Barton and Taylor, 1996; Truelson, 1997; CCME, 1999). Most salmonid embryos will hatch successfully at DO levels between 2 and 3 mg O_2/L to produce small viable larvae, although exposure of fish embryos to levels of oxygen below 2.6 mg O_2/L resulted in incidences of significant abnormal development in some fish, including shortening of vertebral column, jaw deformities, deformed tails and spines, abnormal nervous system and brain development, and other physical deformities (CCME, 1999).

The short-term toxic effects (LC_{50}s) resulting from exposure of invertebrates to low DO are very much species dependent and range from 4.3 mg O_2/L for *Gammarus pulex* (more sensitive) to 0.03 mg O_2/L for *Asellus intermedius*, at temperatures ranging from 10 to 20°C. In tests conducted at lower temperatures (6.4°C), LC_{50}s ranged from 4.4 to 1.7 mg O_2/L for *Callibaetis montanus* and

Neothremma alicia, respectively (AEP, 1997). Nebeker (1972) reported that sensitivity to low DO was directly correlated with temperature, as the 96-hour LC_{50} was 2.9 mg/L at 21°C and 1.0 mg O_2/L (lower sensitivity) at 10°C for the caddis fly, *Hydropsyche betteni*.

For chronic invertebrate studies (>7 days), the Lowest-Observed-Effect Levels (LOELs) ranged from 2.2 mg O_2/L for reproduction in *Daphnia pulex* to <0.2 mg O_2/L for survival in *Gammarus lacustris* (AEP, 1997). There were few identified studies examining the effect of DO on the emergence of adults from juvenile stages. Nebeker (1972) investigated this effect in a 30-day test at 18.5°C on larvae of stoneflies, mayflies, caddis flies and midges and observed the greatest sensitivity in the mayflies, with a reported 30% decline in adult emergence for *Leptophlebia nebulosa* at 9.0 mg O_2/L, an 80% decline at 6.0 mg O_2/L and no emergence at less than 2.4 mg O_2/L. Many of these invertebrate species are important food for other organisms; for some species, the embryos and larvae can overwinter in the sediment layers before emergence in the spring (Barton and Taylor, 1996; Weiss, 1996; Beak International Inc., 1997; The Kali Project, 1999).

The requirement of aquatic species for DO under cold weather conditions is less evident. Cold water can absorb DO to a greater extent than warm water. At 101.3 kPa and 20°C, the saturation point for DO in water is 9.08 mg O_2/L; at 5°C, it is 12.76 mg O_2/L (Tchobanoglous and Burton, 1990). Lowell and Culp (1996) examined survival and behaviour in the mayfly, *Baetis tricaudata*, at low temperatures under different oxygen regimes and under concentrations of bleached kraft pulp mill effluent and municipal sewage. The results indicated that low DO levels in the stream have a greater negative impact on mayfly behaviour and survival than the contaminants in a 1% effluent. The 14-day experiment, conducted at 4.5°C and low DO (5 mg/L), caused the mayflies to move to regions of higher current velocity and significantly reduced their feeding rate and survival. All effects were apparently attributable to low DO, since survival was significantly enhanced for mayflies exposed to the combination of a 1% effluent and high DO (Lowell and Culp, 1996).

2.4.2 Abiotic atmospheric effects

Worst-case calculations were made to determine if ethylene glycol has the potential to contribute to the depletion of stratospheric ozone, ground-level ozone formation or climate change (Bunce, 1996).

The Ozone Depletion Potential (ODP) was calculated to be 0 (relative to the reference compound CFC-11, which has an ODP of 1), as ethylene glycol is not a halogenated compound. It does not, therefore, contribute to the depletion of the stratospheric ozone layer.

The Global Warming Potential (GWP) was calculated to be 1.9×10^{-4} (relative to the reference compound CFC-11, which has a GWP of 1), based on the following formula (Bunce, 1996):

$$GWP = (t_{\text{ethylene glycol}}/t_{\text{CFC-11}}) \times (M_{\text{CFC-11}}/M_{\text{ethylene glycol}}) \times (S_{\text{ethylene glycol}}/S_{\text{CFC-11}})$$

where:

- $t_{\text{ethylene glycol}}$ is the lifetime of ethylene glycol (5.1×10^{-3} years),

- t_{CFC-11} is the lifetime of CFC-11 (60 years),
- M_{CFC-11} is the molecular weight of CFC-11 (137.5 g/mol),
- $M_{ethylene\ glycol}$ is the molecular weight of ethylene glycol (62.07 g/mol),
- $S_{ethylene\ glycol}$ is the infrared absorption strength of ethylene glycol (2389/cm^2 per atmosphere, default), and
- S_{CFC-11} is the infrared absorption strength of CFC-11 (2389/cm^2 per atmosphere).

Based on the above, ethylene glycol does not contribute to climate change.

The Photochemical Ozone Creation Potential (POCP) was estimated to be 41 (relative to the value of an equal mass of the reference compound ethene, which has a POCP of 100), based on the following formula (Bunce, 1996):

$$POCP = (k_{ethylene\ glycol}/k_{ethene}) \times (M_{ethene}/M_{ethylene\ glycol}) \times 100$$

where:

- $k_{ethylene\ glycol}$ is the rate constant for reaction of ethylene glycol with OH radicals (7.7×10^{-12} cm^3/mol per second),
- k_{ethene} is the rate constant for reaction of ethene with OH radicals (8.5×10^{-12} cm^3/mol per second),
- M_{ethene} is the molecular weight of ethene (28 g/mol), and
- $M_{ethylene\ glycol}$ is the molecular weight of ethylene glycol (62.07 g/mol).

This result, together with the fact that rates of emission of ethylene glycol to the atmosphere in Canada are low in relation to rates for other chemicals known to be involved in ozone formation, indicates that ethylene glycol does not contribute significantly to ground-level ozone creation.

2.4.3 Experimental animals and in vitro

The toxicity of ethylene glycol has been investigated most extensively following exposure via the oral route. Where identified, data concerning effects following inhalation and/or dermal exposure are also summarized in this section.

2.4.3.1 Acute toxicity

Ethylene glycol has low acute toxicity via oral, inhalation or dermal exposure. LD_{50}s for the oral administration of ethylene glycol in rats range from 4000 to 10 020 mg/kg-bw, while reported values in guinea pigs and mice are 6610 mg/kg-bw and 5500–8350 mg/kg-bw, respectively. The minimum lethal oral dose in rats is 3.8 g/kg-bw (Clark *et al.*, 1979). Oral LD_{50}s of 5500 and 1650 mg ethylene glycol/kg-bw have also been reported in dogs and cats, respectively. A dermal LD_{50} of 10 600 mg/kg-bw has been reported for rabbits. In rats and mice, the lethal concentration following inhalation exposure has been reported to be >200 mg/m^3.

Signs of acute ingestion of ethylene glycol are dose dependent and include central nervous system depression, paralysis, ataxia, respiratory arrest, tachycardia, tachypnea, coma and death (BUA, 1994). Based on numerous case studies of accidental acute ingestion of ethylene glycol in various animal species, metabolic acidosis has been consistently observed; morphologically, congestion and hemorrhage in the lungs, hemorrhage in the stomach, degeneration in the renal tubules, focal necrosis in the liver and calcium oxalate in the kidneys and brain have been reported (DFG, 1991; BUA, 1994).

In identified toxicological studies concerning the acute oral administration of ethylene glycol in experimental animals, only histopathology in selected organs (i.e., kidney, liver and heart), serum clinical chemistry and urinary parameters have been assessed. In several studies, microscopic changes in the kidney and calcium oxalate crystals in the urine have been observed in dogs (both sexes) exposed by acute peroral administration to either ethylene glycol or commercial antifreeze (containing 95% ethylene glycol) (Riley *et al.*, 1982; Grauer *et al.*, 1984, 1987; Foit *et al.*, 1985; Adams *et al.*, 1989; Smith *et al.*, 1990). Histopathological lesions observed in the kidney included mild tubular nephrosis, necrosis, sloughing of cells, vacuolation and deposition of oxalate crystals in the cortex and medulla. Microscopic myocardial changes have also been noted in rats following acute oral administration (by gavage) of ethylene glycol (7.2 g/kg-bw), including mitochondrial swelling, myofibrillar edema and necrosis, and enlargement of the smooth endoplasmic reticulum (Bielnik and Szram, 1992; Bielnik *et al.*, 1992). Acute oral exposure (by gavage or ingestion) of ethylene glycol or commercial antifreeze in dogs and cats has resulted in ataxia, central nervous system depression, vomiting, polydipsia, metabolic acidosis, alterations in hematological, serum chemistry and urinary parameters, and diminished renal excretory function (Grauer *et al.*, 1984; Thrall *et al.*, 1984).

2.4.3.2 Irritation and sensitization

Studies were not identified concerning the potential of ethylene glycol to induce sensitization in experimental animals. Based on the small number of dermal studies identified (rabbits and guinea pigs only), ethylene glycol induced only mild dermal irritation (Clark *et al.*, 1979; Guillot *et al.*, 1982; Anderson *et al.*, 1986). Studies in rabbits and humans indicate that acute or short-term ocular exposure to ethylene glycol (liquid or vapour) produces minimal conjunctival irritation without permanent corneal damage (McDonald *et al.*, 1972; Clark *et al.*, 1979; Guillot *et al.*, 1982; Grant and Schuman, 1993).

2.4.3.3 Short-term and subchronic repeated dose toxicity

In a 10-day study in which a wide range of endpoints was examined in Sprague Dawley rats ($n = 10$ per sex per dose) administered drinking water containing 0.5–4.0% ethylene glycol (650–5300 mg/kg-bw per day in males; 800–7300 mg/kg-bw per day in females), significant ($p < 0.05$) alterations in serum chemistry parameters were observed at all doses in males and at ≥1500 mg/kg-bw per day in females (Robinson *et al.*, 1990). The incidence and severity of histopathological lesions in the kidney (including dilation, degeneration, necrosis, inflammation, calcium oxalate crystals and proteinaceous material) were significantly ($p < 0.05$) increased in males at ≥2600 mg/kg-bw per day and in females at 7300 mg/kg-bw per day.

In a 4-week study in which Wistar rats were administered (by gavage) 2000 mg ethylene glycol/kg-bw per day, effects in the kidney (including discoloration, tubulopathy, hyperplasia and crystalline deposits), changes in urinary parameters (including calcium oxalate in urine) and increased relative kidney weights (10–14%) were observed in both sexes (Schladt *et al.*, 1998).

In studies in which groups (n = 5–10 per sex) of $B6C3F_1$ mice were administered (by gavage) 50, 100 or 250 mg ethylene glycol/kg-bw per day (in water) for 4 days, no clear treatment-related effects on survival, relative organ weights, hematology or histopathology in major organs (including the liver, kidney, lung and bone marrow) were observed, compared with untreated controls. However, exposure produced effects in the bone marrow, including depression of progenitor cells at all doses (males, $p < 0.01$–0.05), hypocellularity at ≥100 mg ethylene glycol/kg-bw per day (both sexes, $p < 0.01$–0.05) and erythropoiesis at 250 mg/kg-bw per day (males, $p < 0.05$) (Hong *et al.*, 1988). As indicated above, resulting effects on hematological parameters were not observed; hence, the biological significance of these effects is unclear.

In a limited study in which macaque monkeys were exposed to 0.25–10% (1–152 g/kg-bw) ethylene glycol in drinking water for 6–157 days, dose-related renal effects (including necrosis and calcium oxalate deposition in proximal tubules) were observed among males ingesting ≥17 g ethylene glycol/kg-bw (Roberts and Seibold, 1969). No renal histopathology was observed among females receiving ≥19 g ethylene glycol/kg-bw.

In subchronic investigations conducted in rats and mice, in which a wide range of endpoints (survival, body weight, hematology, clinical chemistry, organ weights, histopathology) have been examined following oral exposure to ethylene glycol (either in the diet or in drinking water), microscopic changes in the kidney have consistently been observed at lowest doses, with the severity of renal effects generally appearing greater in males than in females (Gaunt *et al.*, 1974; Melnick, 1984; Robinson *et al.*, 1990; NTP, 1993).

In a 90-day study in which Sprague-Dawley rats ingested drinking water containing 0.25–2.0% ethylene glycol (205–3130 mg/kg-bw per day in males; 600–5750 mg/kg-bw per day in females), alterations in hematological parameters in females ($p < 0.05$) were observed at lowest doses (i.e., 600 mg/kg-bw per day) (Robinson *et al.*, 1990); hematological effects have generally not been observed in other subchronic (or chronic) oral studies in rats (Blood, 1965; Gaunt *et al.*, 1974; Melnick, 1984; NTP, 1993). At higher oral doses in this study, there were increased relative kidney weights ($p < 0.05$) in males at ≥950 mg/kg-bw per day, decreased body weights ($p < 0.05$) in males at 3130 mg/kg-bw per day and dose-related histopathological changes ($p < 0.05$) in the kidney in males (≥950 mg/kg-bw per day) and females (≥3100 mg/kg-bw per day), compared with unexposed controls. Among male rats receiving 0, 205, 410, 950 or 3130 mg ethylene glycol/kg-bw per day, the incidence of specific histological changes within the kidney was 0/10, 0/10, 0/10, 5/10 and 8/9 (tubular dilation); 0/10, 0/10, 0/10, 5/10 and 9/9 (tubular degeneration); and 0/10, 0/10, 0/10, 3/10 and 8/9 (intratubular crystals), respectively (Robinson *et al.*, 1990).

In a well-conducted study in which Fischer 344 rats (both sexes) were administered 165, 325, 640, 1300 or 2600 mg ethylene glycol/kg-bw per day in the diet for 13 weeks, significant effects were observed at 1300 mg/kg-bw per day and above, including reduced growth in males ($p < 0.01$ or $p < 0.05$), increased kidney weight in both sexes ($p < 0.01$), renal histopathology (dilation, necrosis, fibrosis and crystal deposition in renal tubules) in males and alterations in serum clinical chemistry parameters in males ($p < 0.01$ or $p < 0.05$), compared with untreated controls (Melnick, 1984). At 2600 mg/kg-bw per day, in males, mortality was increased and relative thymus weights decreased ($p < 0.05$), and in females, microscopic changes in the kidney (infiltration of inflammatory cells, increased vacuolation and enlarged nuclei in renal tubules) were increased.

In an unpublished study by Gaunt *et al.* (1974), in which a wide range of endpoints was examined in Wistar rats ($n = 25$ per sex per dose) administered ethylene glycol in the diet (males: 35, 71, 180 or 715 mg/kg-bw per day; females: 38, 85, 185 or 1128 mg/kg-bw per day) for up to 16 weeks, statistically significant specific microscopic changes in the kidney (i.e., dilation, degeneration, protein casts, deposition of calcium oxalate crystals in nephrons) were observed at the highest dose. Among male rats receiving 0, 35, 71, 180 or 715 mg ethylene glycol/kg-bw per day for 16 weeks, the incidence of specific histological changes within the kidney was 0/15, 0/15, 0/15, 1/15 and 0/15 (individual nephrons with dilated tubules and protein casts), 0/15, 1/15, 1/15, 2/15 and 5/15 ($p < 0.05$) (individual nephrons with degenerative changes), 0/15, 0/15, 0/15, 1/15 and 4/15 ($p < 0.05$) (individual nephrons with degenerative changes and occasional oxalate crystal), 0/15, 0/15, 0/15, 0/15 and 2/15 (several nephrons with degenerative changes and frequent crystals) and 0/15, 0/15, 0/15, 0/15 and 4/15 ($p < 0.05$) (generalized tubular damage and heavy crystals), respectively. The overall incidence of male rats with tubular damage in groups receiving 0, 35, 71, 180 or 715 mg ethylene glycol/kg-bw per day in the diet for 16 weeks was 0/15, 1/15, 1/15, 4/15 ($p < 0.05$) and 15/15 ($p < 0.001$), respectively. With one exception, severe tubular damage was observed in all male rats having oxalate crystals in the kidney.

Histopathological analyses of the kidneys in small ($n = 5$) groups of animals exposed for 2 or 6 weeks revealed no statistically significant increase in the incidence of specific histological changes, although the overall incidence of animals with tubular damage was significantly elevated ($p < 0.01$) in the high-dose group after 6 weeks' exposure. The occurrence of inflammation of the Harderian gland in the exposed males, "pneumonial changes" in the lungs of males and females, and salivary adenitis was not considered related to exposure to ethylene glycol. An increased incidence of kidney damage (although not statistically significant) was observed among females receiving 1128 mg ethylene glycol/kg-bw per day in the diet, with urinary elimination of oxalic acid also increased ($p < 0.05$) in females at this dose, compared with controls (Gaunt *et al.*, 1974).

In the single identified oral subchronic study in mice, in which a wide range of endpoints was examined in $B6C3F_1$ mice receiving 400–6700 mg ethylene glycol/kg-bw per day in the diet for 13 weeks, treatment-related effects were limited to microscopic changes in the liver (hyaline degeneration) and kidney (minimal to mild tubule dilation, cytoplasmic vacuolation and regenerative hyperplasia) in males at ≥3300 mg/kg-bw per day. There was no evidence of deposition of oxalate crystals in renal tubules. Based on assessment of body and organ weights, clinical chemistry, hematology and urinary

parameters, and gross pathology and histopathology in a wide range of organs, effects were not observed in females exposed to up to 6700 mg ethylene glycol/kg-bw per day, compared with untreated controls (Melnick, 1984; NTP, 1993).

Identified data on effects following inhalation are restricted to a few early, limited, short-term studies. No treatment-related effects on survival, behaviour, physical appearance, locomotor activity, hematology, clinical chemistry parameters or histopathology in selected organs (including lung, kidney and liver) were observed in rats, guinea pigs, rabbits, dogs or monkeys exposed (whole body) to 10 or 57 mg ethylene glycol vapour/m^3 for 8 hours per day, 5 days per week, for 6 weeks (Coon *et al.*, 1970). In a review by Browning (1965), it was reported that no histopathological changes were observed in rats or mice exposed by "repeated inhalation" to 157 ppm (400 mg/m^3). Exposure of rats to 197 ppm (500 mg/m^3) for 28 hours over 5 days resulted in slight narcosis. However, any putative intake of ethylene glycol resulting from the ingestion of this substance deposited on the fur during grooming or via dermal absorption (i.e., see Tyl *et al.*, 1995a,b) was not assessed in these studies.

In subchronic inhalation studies, no clear treatment-related effects on histopathology in the small number of organs examined (including lung, liver and kidney), on hematology or on clinical chemistry parameters were observed in rats (n = 15), guinea pigs (n = 15), rabbits (n = 3), dogs (n = 2) and monkeys (n = 3) exposed continuously to 12 mg ethylene glycol vapour/m^3 for 90 days, compared with unexposed controls (Coon *et al.*, 1970). Although mortality was observed among rabbits (n = 1), guinea pigs (n = 3) and rats (n = 1) exposed in this study, none of the deceased animals was reported to exhibit "any specific signs of toxicity" (Coon *et al.*, 1970). Moderate to severe irritation of the eyes was reported for the continuously exposed rabbits (i.e., erythema, edema, discharge) and rats (i.e., corneal opacity and apparent blindness in 2 of 15 animals); however, these effects were not observed in a separate study involving exposure of these species to 57 mg ethylene glycol/m^3, 8 hours per day, 5 days per week, for 6 weeks (Coon *et al.*, 1970). Any putative intake of ethylene glycol resulting from the ingestion of this substance deposited on the fur during grooming or via dermal absorption (i.e., see Tyl *et al.*, 1995a,b) was not assessed in these studies.

2.4.3.4 Chronic toxicity and carcinogenicity

In a carcinogenicity bioassay reported by DePass *et al.* (1986a), no tumours were observed in Fischer 344 rats (n = 130 per sex per dose) receiving 40, 200 or 1000 mg ethylene glycol/kg-bw per day in the diet for up to 2 years, based on microscopic examination of an extensive range of organs (including kidney, liver and bone marrow). At ≥200 mg/kg-bw per day, calcium oxalate crystals were observed in the urine in both sexes. At 1000 mg/kg-bw per day, females had a (transient) increase in kidney weight ($p < 0.01$) and mild fatty changes in the liver ($p < 0.01$),[1] while males had 100% mortality by 15 months (attributed to calcium oxalate nephrosis), reduced growth ($p < 0.001$), organ weight changes (liver and kidney, $p < 0.001$ or $p < 0.05$), microscopic lesions in the kidney (including dilation, proteinosis,

[1] Information presented in the text, although not in Table 6 of the published account of this study (DePass *et al*, 1986a), indicated that the incidence of fatty metamorphosis in the liver of female rats receiving 200 mg/kg-bw per day was significantly increased, compared with the controls.

glomerular shrinkage, hyperplasia, nephritis, $p < 0.001$) and alterations in hematological, clinical chemistry and urinary parameters ($p < 0.001$ to $p < 0.05$). Among male rats receiving 0, 40, 200 or 1000 mg ethylene glycol/kg-bw per day, the incidence of specific histological changes within the kidney was 0/256, 0/129, 1/129 and 10/116 ($p < 0.001$) (tubular dilation), 5/256, 0/129, 3/129 and 72/116 ($p < 0.001$) (hydronephrosis), 0/256, 0/129, 0/129 and 95/116 ($p < 0.001$) (oxalate nephrosis) and 0/256, 0/129, 0/129 and 16/116 ($p < 0.001$) (calcium oxalate crystalluria), respectively. After 18 months on study, all male rats in the high-dose group either had died or were sacrificed when moribund (due to calcium oxalate nephrosis), which complicates both presentation and interpretation of the data on the incidence of renal lesions among the high-dose male rats in this study. Data on the overall (total) incidence of renal damage associated with exposure to ethylene glycol were not provided in the published account of this study.

Histological reporting for non-cancer lesions in the published report of this study was inadequate due to lack of application of consistent diagnostic criteria to assess the onset and progression of treatment-related histopathological changes[2]. Terminology, for example, for intermediate and end stage histological renal lesions was inconsistent and as a result, the incidence of early stage lesions was inadequately reported and likely considerably underestimated. (Based on comparison with additional data provided by the study sponsor (Snellings, personal communication, 2000), the incidences of early stage lesions such as calcium oxalate crystalluria presented in the published paper represent the numbers of animals from interim sacrifices in which lesions were observed (numerators) over the total number of animals on test (denominators) since they were not reported at later stages[3] (Table 14). More appropriately, consistent terminology would have been applied across the study with an indication of severity over time. Moreover, after 18 months on study, all male rats in the high-dose group had either died or were sacrificed when moribund (due to calcium oxalate nephrosis), which complicates both presentation and interpretation of the data on the incidence of renal lesions amongst the high-dose male rats in this study and decreases the sensitivity of the bioassay for assessing carcinogenicity

In an early investigation in which small groups of Sprague-Dawley rats (n = 16 per sex per dose) were fed diets containing 0.1–4% ethylene glycol (50–2000 mg/kg-bw per day) for 2 years, absolute organ weights were reduced for the liver (9–17%), lungs (24–34%) and kidneys (19–24%) in males at all doses (i.e., ≥50 mg/kg-bw per day) (Blood, 1965). The reductions in absolute kidney weight reported in this study are inconsistent with observed increases in kidney weights in several more recent studies conducted in rats by the same route of exposure (Melnick, 1984; DePass *et al.*, 1986a; Robinson *et al.*, 1990; Schladt *et al.*, 1998). For the lungs and liver, the reductions in organ weight were not dose related. Data on relative organ weights and statistical analyses were not provided in the published account of this study. Renal histopathology (calcification and/or oxalate-containing calculi), reduced growth and mortality were observed in both sexes at ≥250 mg/kg-bw per day, with effects

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[2] Based in part on information presented in Maronpot (2000a) and Ohanian (2000).

[3] Slides from the 6 and 12 month sacrifices were read by a different pathologist than those from the 18 and 24 month sacrifices. (Maronpot, 2000b)

consistently observed at lower doses in males than in females (Blood, 1965). No tumours were observed in the limited number of tissues examined (including liver, kidney and lung).

Similarly, no increase in the incidence of tumours was presented in an early (limited) chronic bioassay in which only survival, growth and histopathology in selected organs were examined in small groups of male (n = 6 per group) and female (n = 4 per group) albino rats (strain not specified) fed diets containing 1% or 2% ethylene glycol (500 or 1000 mg/kg-bw per day) for 2 years (Morris *et al.*, 1942). Exposure to 500 or 1000 mg ethylene glycol/kg-bw per day produced bladder stones in males (although not dose related), marked renal histopathology (including deposition of calcium oxalate, glomerular atrophy, tubular casts, lymphocytic infiltration and fibrosis) in both sexes, and slight liver damage (diffuse or centrilobular atrophy, bile duct proliferation and fatty degeneration) in both sexes, compared with untreated controls.

In an extensive NTP (1993) bioassay, no tumours were observed in B6C3F_1 mice (n = 60 per sex per dose) administered ethylene glycol in the diet (males: 1500, 3000 or 6000 mg/kg-bw per day; females: 3000, 6000 or 12 000 mg/kg-bw per day) for 103 weeks, based on microscopic examination of a wide range of organs (including bone marrow, kidney, liver and lung) at 15 months and 2 years. Females had a treatment-related increase in arterial medial hyperplasia in the lungs ($p \leq 0.05$ or $p \leq 0.01$) at all levels of exposure and hyaline degeneration in the liver ($p \leq 0.01$) at 12 000 mg/kg-bw per day. At 3000 and 6000 mg/kg-bw per day, male mice had dose-related hepatocellular hyaline degeneration ($p \leq 0.01$) and transient kidney damage (nephropathy; $p \leq 0.05$), compared with untreated controls. No clear evidence of treatment-related effects on survival, body weight or tissue histopathology was observed in CD-1 mice (n = 80 per sex per dose) given 40, 200 or 1000 mg ethylene glycol/kg-bw per day in the diet for 2 years, based on microscopic examination of an extensive range of organs (including kidney, lungs and liver) at 80 weeks and 2 years, while organ weights and hematological and clinical chemistry parameters were not assessed (DePass *et al.*, 1986a). However, as indicated above in relation to the bioassay in rats reported by the same authors, histological reporting in this study was inadequate.

In a limited early investigation reported by Blood *et al.* (1962), male (n = 2) and female (n = 1) rhesus monkeys receiving 80 or 200 mg ethylene glycol/kg-bw per day in the diet, respectively, for 3 years had no overt signs of toxicity and no abnormal calcium deposits or histopathological changes in the major tissues examined (including the urogenital system, liver and bone marrow). However, the results of this study are limited by the small number of animals used, the small number of endpoints examined and the absence of untreated controls.

In the only identified investigation conducted by the dermal route, no clear treatment-related effects were observed in female Swiss mice following dermal application of ethylene glycol (unspecified volume) twice weekly for 43 weeks (Berenblum and Haran, 1955). However, interpretation of the results of this study is limited by the incomplete description of the protocol, the lack of untreated controls, the small number of animals and the limited number of parameters examined (i.e., gross examination of unspecified organs and microscopic examination of gross lesions only).

In two studies conducted by subcutaneous injection, no tumours were observed in Fischer 344 rats (Mason *et al.*, 1971) or NMRI mice (Dunkelberg, 1987) following repeated administration of up to 1000 mg ethylene glycol/kg-bw for 52 or 106 weeks, based on examination of selected tissues (including liver, lung and skin).

2.4.3.5 Genotoxicity

In *in vitro* mutagenicity studies conducted in bacterial cells, results have been consistently negative (Clark *et al.*, 1979; Pfeiffer and Dunkelberg, 1980; Zeiger *et al.*, 1987; JETOC, 1996), with and without S9 activation. Results have also been negative for mutagenicity in mouse lymphoma L51784Y cells (with and without activation) (McGregor *et al.*, 1991), with positive results observed in this test system in conjunction with cytotoxicity (Brown *et al.*, 1980). Results have been negative for chromosomal aberrations and sister chromatid exchange in cultured Chinese hamster ovary cells (with and without activation) (NTP, 1993) and for DNA damage in rat hepatocytes (Storer *et al.*, 1996) and *Escherichia coli* (McCarroll *et al.*, 1981; von der Hude *et al.*, 1988).

In *in vivo* genotoxicity studies, results have been negative for dominant lethal mutations in F344 rats following administration in F_2 males (from a multigeneration study) of up to 1000 mg ethylene glycol/kg-bw per day for 155 days (DePass *et al.*, 1986b). Results have also been negative for chromosomal aberrations in bone marrow cells of male Swiss mice exposed (by intraperitoneal injection) to 638 mg ethylene glycol/kg-bw per day for 2 days (Conan *et al.*, 1979). There was only a slight increase in the incidence of micronuclei in the erythrocytes of Swiss mice administered ≥1250 mg ethylene glycol/kg-bw by gavage (or by intraperitoneal injection) (Conan *et al.*, 1979). However, it should be noted that the magnitude of the effect was small, was not dose related and was based on pooled data for treated groups.

2.4.3.6 Reproductive and developmental toxicity

In a three-generation reproduction study in which F344 rats (both sexes) received 40, 200 or 1000 mg ethylene glycol/kg-bw per day in the diet, there were no treatment-related parental effects (based on survival, body weight, food consumption, appearance, behaviour and histopathology in major organs) or reproductive or developmental toxicity in offspring (based on fertility index, gestation index, gestation survival index, pup weight, appearance, behaviour and histopathology in major organs), compared with untreated controls (DePass *et al.*, 1986b).

In a study in which a wide range of endpoints was examined in F344 rats administered 40, 200 or 1000 mg ethylene glycol/kg-bw per day in the diet during days 6–15 of gestation, statistically significant increases in developmental effects were limited to that ($p < 0.001$) for poorly ossified and unossified vertebral centra in the offspring of dams exposed to 1000 mg ethylene glycol/kg-bw per day, compared with controls (Maronpot *et al.*, 1983). Exposure to ethylene glycol had no effect upon the reproductive parameters examined (i.e., pregnancy rate, number of corpora lutea, number of litters, live

and dead fetuses, total implantations, pre-implantation loss and resorptions); there was also no evidence of maternal toxicity.

In studies in which pregnant CD rats were administered (by gavage) 150, 500, 1000 or 2500 mg ethylene glycol/kg-bw per day on days 6–15 of gestation, significant ($p < 0.05$ or $p < 0.01$) dose-related developmental effects were observed at 1000 mg/kg-bw per day and above, including reduced fetal body weight per litter, reduced skeletal ossification and malformations in the skeleton (missing arches, missing and extra ribs) (Neeper-Bradley *et al.*, 1995). Exposure had no effect upon the reproductive parameters examined (i.e., number of corpora lutea, live and dead fetuses, and resorption sites), compared with controls. Maternal toxicity was observed at 2500 mg/kg-bw per day, based on an increase (10%, $p < 0.001$) in relative kidney weight, compared with controls.

Other oral studies conducted in rats (Price *et al.*, 1985; Yin *et al.*, 1986; Myers *et al.*, 1988; Marr *et al.*, 1992) do not contribute additionally to the weight of evidence or dose–response for the developmental/reproductive toxicity of ethylene glycol, due to inclusion of few endpoints or the absence of data on maternal toxicity (Yin *et al.*, 1986) or conduct of the studies at very high doses at which there was clear evidence of maternal toxicity (>1250 mg/kg-bw per day by stomach tube) (Price *et al.*, 1985; Marr *et al.*, 1992).

In a continuous breeding study in which male and female CD-1 mice received 410, 840 or 1640 mg ethylene glycol/kg-bw per day in drinking water, treatment-related developmental effects (i.e., decreased F_1 female pup weight, $p < 0.05$) were observed at ≥840 mg/kg-bw per day (Lamb *et al.*, 1985; Morrissey *et al.*, 1989). Only slight reproductive effects were observed at 1640 mg/kg-bw per day, based on slight reductions in the number of F_1 litters per fertile pair (8%, $p < 0.01$) and number of live F_1 pups per litter (6%, $p < 0.05$), compared with controls. Malformations were also observed in F_1 offspring (including unusual facial features and skeletal changes in the skull, sternebrae, ribs and vertebrae) at 1640 mg/kg-bw per day, compared with controls; however, incidence rates were not reported. No parental toxicity was observed following exposure to ethylene glycol, based on examination of survival, body weight gain, water intake and overt signs of toxicity (Lamb *et al.*, 1985; Morrissey *et al.*, 1989).

Following administration (by gavage) in pregnant CD-1 mice of 750–3000 mg ethylene glycol/kg-bw per day during days 6–15 of gestation, there was a dose-related reduction in average fetal body weights per litter (9–27%, $p < 0.01$) and marked dose-related increases in the incidence of malformed live fetuses per litter (0.25% in the controls and 10–57% in treated groups, $p < 0.01$), litters with malformed fetuses (4% in the controls and 67–96% in treated groups, $p < 0.001$), and skeletal malformations in the ribs, arches, centra and sternebrae (4% in controls and 63–96% in treated groups, $p < 0.001$) (Price *et al.*, 1985). Exposure had no effect on reproductive indices, including the number of implantations, resorption sites, or live and dead fetuses, compared with untreated controls. Maternal toxicity was evident at 1500 mg/kg-bw per day and above, based on a significant decrease in maternal body weight gain during treatment (32%, $p < 0.01$) and absolute liver weight (9%, $p < 0.01$), compared with controls.

In studies in which pregnant CD-1 mice were administered (by gavage) 0, 50, 150, 500 or 1500 mg ethylene glycol/kg-bw per day on days 6–15 of gestation (Neeper-Bradley *et al.*, 1995), exposure to the highest dose produced a statistically significant (i.e., $p < 0.01$ or $p < 0.05$) increase in the incidence of 25 of the 27 skeletal malformations/variations examined, compared with unexposed controls. At 1500 mg/kg-bw per day, an increased incidence of skeletal malformations (e.g., fused or extra centra, arches and ribs, $p < 0.01$) and variations (e.g., reduced ossification in centra and phalanges, enlargement of fontanel and sagittal suture in the skull) and a reduction in fetal body weight per litter ($p < 0.01$) were observed. The administration of 500 (and 1500) mg ethylene glycol/kg-bw produced a statistically significant ($p < 0.01$) increase in the incidence of one skeletal change, the occurrence of an extra 14th rib on the first lumbar arch. In mice administered 0, 50, 150, 500 or 1500 mg ethylene glycol/kg-bw per day, the incidence of this specific skeletal change (expressed either as the occurrence in litter/total litters examined or as the occurrence in fetus/total fetuses examined) was 4/19, 4/20, 6/24, 17/24 ($p < 0.01$) and 21/21 ($p < 0.01$), and 5/201, 11/223, 13/278, 75/266 and 128/235, respectively. Exposure produced no treatment-related effects on reproductive parameters (including the number of corpora lutea, viable implantation sites, pre-implantation loss or sex ratio) or maternal toxicity.

In a study in which only selected reproductive endpoints (including sperm counts and motility, histopathology and organ weights in the testes and epididymis, percentage of pregnant females, and number of live and dead implantation sites) were examined in CD-1 mice exposed (both sexes) by gavage to 250–2500 mg ethylene glycol/kg-bw per day, significant treatment-related effects ($p < 0.05$) were observed at the highest dose only and were limited to a reduction in live implantations per female and an increase in dead implantations per female, compared with controls (Harris *et al.*, 1992). No signs of parental toxicity were observed, based on examination of survival, body weight, clinical signs and histopathology in selected organs (including liver and kidney).

In a limited reproductive toxicity study, in which only histopathology and organ weights in the testes and "vesicular and coagulating glands" and hematological parameters were examined in males of an unspecified strain of mice orally exposed (presumably by gavage) to 500–4000 mg ethylene glycol/kg-bw per day for 5 weeks, no treatment-related effects were observed, compared with untreated controls (Nagano *et al.*, 1973).

Other oral studies conducted in mice (Morrissey *et al.*, 1989; Harris *et al.*, 1992) do not contribute additionally to the weight of evidence of developmental/reproductive toxicity of ethylene glycol, due to the absence of data on maternal toxicity or conduct of the studies at higher doses than used in similar studies addressed herein.

A single study has been identified in which the developmental and reproductive toxicities of ethylene glycol have been examined in rabbits following oral exposure. Despite the presence of severe maternal toxicity (mortality and degenerative changes in the kidney) at the highest dose level, there was no evidence of developmental or reproductive effects in fetuses derived from New Zealand white rabbits administered (by gavage) 100–2000 mg ethylene glycol/kg-bw per day during days 6–19 of gestation (Tyl *et al.*, 1993). Parameters examined included the number of corpora lutea, pre- and post-

implantation loss, number of fetuses, fetal body weight per litter, litter sex ratio, or external, visceral or skeletal variations or malformations.

Identified inhalation studies conducted in CD rats and CD-1 mice, in which pregnant animals were exposed (whole body) to up to 2090 mg ethylene glycol/m^3 for 6 hours per day on days 6–15 of gestation, provide some evidence of treatment-related developmental effects, including skeletal variations (reduced ossification, extra ribs, dilated lateral ventricles, malaligned centra) and malformations of the head (exencephaly), face (cleft palate, abnormal face and facial bones) and skeleton (vertebral fusion, and fused, forked, missing and extra ribs) (Tyl *et al.*, 1995a,b). However, in each of these studies, there was likely considerable intake due to ingestion after grooming and/or percutaneous absorption; it was estimated by the authors that rats and mice received at least 620 mg/kg-bw per day and 910–1400 mg/kg-bw per day, respectively, in this manner. Thus, these studies do not allow for a clear conclusion concerning the role of inhaled ethylene glycol in the induction of developmental toxicity in these species. It is noteworthy that developmental effects observed in these studies (likely due to ingestion of ethylene glycol) are similar to those observed in oral developmental toxicity studies (Lamb *et al.*, 1985; Price *et al.*, 1985; Morrissey *et al.*, 1989; Neeper-Bradley *et al.*, 1995) in the same strains of rats and mice (i.e., CD and CD-1, respectively).

In a "nose-only" inhalation study, exposure of pregnant CD-1 mice to 360, 779 or 2505 mg ethylene glycol/m^3 for 6 hours per day on days 6–15 of gestation yielded increases in some skeletal variations (e.g., decreased ossification in centra and sternebrae, unossified phalanges of the forelimb, extra ribs, extra ossification site in the skull)[4] and a statistically significant ($p < 0.05$) 8-fold increase in the number of litters with animals exhibiting 2–12 fused ribs at the highest concentration (i.e., 2505 mg/m^3), compared with controls (the control exposure atmosphere for both the nose-only and whole-body groups was water aerosol) (Tyl *et al.*, 1995b). Ethylene glycol had no effect upon the incidence of external or visceral malformations or reproductive parameters (including number of corpora lutea, total and viable implantations per litter, pre- and post-implantation loss and sex ratio), compared with controls. Only minimal maternal toxicity was observed at 2505 mg/m^3, based on a slight increase (7%, $p < 0.05$) in relative kidney weight, without evidence of cellular injury. The results of this study support the hypothesis that developmental effects observed in whole-body inhalation studies are due principally to systemic exposure (via ingestion or dermal absorption), since limiting exposure from these systemic routes prevented most of the effects observed in mice following whole-body inhalation exposure.

In the single dermal study identified, in which pregnant CD-1 mice were exposed (by occluded cutaneous application) to aqueous solutions of 0, 12.5, 50 or 100% ethylene glycol (estimated doses of 0, 400, 1700 or 3500 mg/kg-bw per day) during days 6–15 of gestation, reported effects were limited to maternal toxicity (based on minimal-grade renal lesions and increased corrected gestational body weight change) and a significant increase ($p < 0.05$) in two skeletal variations (i.e., poorly ossified skull bone and unossified intermediate phalanges of the hindlimb) at 3500 mg/kg-bw per day (Tyl *et al.*, 1995c). However, the investigators were unclear as to whether these skeletal effects were treatment

[4] Statistical analysis was not provided.

related or incidental. Compared with untreated controls, dermal exposure to ethylene glycol had no effect upon the reproductive indices examined, including the number of corpora lutea, implantation and resorption sites, and live and dead fetuses.

2.4.3.7 Neurological effects and effects on the immune system

Although data are limited, results of identified toxicity studies conducted (via oral, inhalation or dermal routes) in rodents, rabbits and monkeys do not indicate that neurological or immunological effects are critical endpoints for ethylene glycol. Neurological effects have not been observed at doses below those that have induced renal toxicity (Penumarthy and Oehme, 1975; Clark *et al.*, 1979; Grauer *et al.*, 1987), and consistent treatment-related effects on immune system-related parameters have not been observed in available repeated-dose toxicity studies in which several species have been exposed to ethylene glycol either orally or by inhalation.

Although the significance of the development of histological changes in the kidney of rats exposed over the long term to low levels of ethylene glycol is unclear, some data on the nature of early-stage renal response have been reported. Using immunohistochemical techniques, de Water *et al.* (1999) observed the recruitment of monocytes, macrophages and giant multinucleated macrophage-derived cells to sites of calcium oxalate crystal deposition in the renal interstitium of male Wistar rats administered drinking water containing high levels (i.e., 8 g/litre) of ethylene glycol (and ammonium chloride) for 7–9 days.

2.4.3.8 Toxicokinetics and mode of action

There is convincing evidence that the toxicological effects observed in laboratory animals exposed to ethylene glycol, as well as the adverse health effects in humans exposed acutely to this substance, are due primarily to the actions of one or more of its metabolites, rather than to the parent compound *per se*. In studies in which inhibitors of alcohol dehydrogenase (the enzyme catalysing the first rate-limiting step in the metabolism of ethylene glycol) have been administered in both animals and humans, toxicity has been minimized. In laboratory animals, the concurrent ingestion or infusion of ethanol, pyrazole or 4-methylpyrazole prevents the renal toxicity and mortality observed following exposure to ethylene glycol (Grauer *et al.*, 1987; U.S. EPA, 1987). In humans, typical therapies for acute ethylene glycol poisoning have included hemodialysis and the administration of ethanol (to inhibit ethylene glycol metabolism by competition for alcohol dehydrogenase activity) and sodium bicarbonate (to reduce metabolic acidosis) (Jacobsen and McMartin, 1986; Grant and Schuman, 1993). More recent treatments for acute ethylene glycol poisoning in humans have involved the administration of 4-methylpyrazole (Brent *et al.*, 1999), a potent inhibitor of the human alcohol dehydrogenase enzyme (Dawidek-Pietryka *et al.*, 1998).

Based upon the available information, toxicological effects resulting from exposure to ethylene glycol may involve one or a combination of the following: development of an increased osmolal gap,[5] development of metabolic acidosis,[6] the formation of calcium oxalate crystals[7] and their deposition in various tissues and/or possible direct toxic effects produced by one or more of its metabolites. This discussion focuses on the mode of induction of critical effects — i.e., those on the kidneys of experimental animals (rats) and humans and developmental effects.

A mode of action involving the formation and deposition of calcium oxalate crystals as requisite steps in the induction of renal effects in animals and humans is consistent with available metabolic and histopathological data. For example, species differences in sensitivity to renal effects are consistent with the limited available data on the comparative proportions of ethylene glycol excreted as oxalic acid, these being greater in rats than in mice (7–8% versus not detected at 24 hours; Frantz *et al.*, 1996a,b). Based on limited information, values for monkeys are intermediate, i.e., between those for rats and mice (0.3% at 48 hours; McChesney *et al.*, 1971), and those for humans are within the range of values reported for rats (Reif, 1950).

Indeed, calcium oxalate crystals are considered to be important etiological agents in the development of the renal failure in humans acutely poisoned by the ingestion of ethylene glycol (Jacobsen and McMartin, 1986; Wiley, 1999). In addition, in almost all cases where examined, extensive renal damage in experimental animals has been observed only where such crystals are present (Gaunt *et al.*, 1974; Melnick, 1984). Also, in all cases where examined, ethylene glycol-associated renal damage has been observed only at doses greater than those at which there were increases in urinary excretion of oxalate or calcium oxalate crystals (Gaunt *et al.*, 1974; DePass *et al.*, 1986a). However, while most evidence implicates oxalate in the induction of renal damage, on the basis of currently available information, the possible role of less frequently observed hippuric acid crystals and direct cytotoxicity of other metabolites such as glycoaldehyde, glycolic acid and glyoxylic acid cannot be precluded (Parry and Wallach, 1974; Marshall, 1982).

Sex-related variations in sensitivity to the renal effects of ethylene glycol may be a function of both toxicokinetic and toxicodynamic differences. Although there have been variations in the proportion of metabolites excreted as oxalic acid in male versus female rats in repeated-dose studies, proportions have been similar following single administration. In Sprague-Dawley rats administered (orally via gavage) a single dose of 1000 mg [^{14}C]ethylene glycol/kg-bw, similar amounts of the administered

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[5] In the initial stages following systemic exposure to ethylene glycol, the concentration of ethylene glycol in extracellular fluids increases, leading to increased osmolality, hyperosmolality and an increased osmolal gap.

[6] The accumulation of acidic products (e.g., glycolic acid, oxalic acid and lactic acid) due to the metabolism of ethylene glycol results in metabolic acidosis, a state that is characterized by an actual or relative decrease of alkali in body fluids in relation to acid content. The major determinant of acidosis is the degree of glycolic acid accumulation in the blood.

[7] Although only a minor metabolite, oxalic acid is of toxicological significance since it chelates with calcium ions, resulting in the precipitation of (insoluble) calcium oxalate monohydrate in tissues (notably, in the kidney and brain).

radioactivity (i.e., 7–8%) were eliminated in the urine as [^{14}C]oxalic acid in the males and females (Frantz *et al.*, 1996a,b). Similar amounts of radioactivity have been measured in the kidneys of male and female rats administered single doses of [^{14}C]ethylene glycol (Frantz *et al.*, 1996a,b). In two studies in which Sprague-Dawley rats were provided drinking water containing 0.5% ethylene glycol for 28 days, the elimination of oxalic acid (expressed as either mg or µM per 24 hours) in the urine was approximately 2.6- and 4.3-fold higher in males than in females (Lee *et al.*, 1992, 1996).[8] In a study in which male and female Wistar rats received similar doses (i.e., from 35 to 180 mg/kg-bw per day) of ethylene glycol from the diet over a 14- to 16-week period, slightly lower (i.e., 1.3- to 2.8-fold) levels of oxalic acid were excreted in the urine of females than in that of males (Gaunt *et al.*, 1974).

In male Sprague-Dawley rats administered drinking water containing 0.5% ethylene glycol for 28 days, the occurrence of kidney stones (as well as the excretion of oxalic acid in the urine) was reduced in castrated males, compared with controls (Lee *et al.*, 1992, 1996). The effects of castration upon kidney stone formation (and excretion of oxalic acid) were reversed by the administration of exogenous testosterone to the castrated animals (Lee *et al.*, 1996). Based upon the results of a study using an ethylene glycol/vitamin D induced urolithiasis model in oophorectomized Wistar female rats, Iguchi *et al.* (1999) suggested that the sex-related differences in the occurrence of kidney stones in rats administered ethylene glycol may be attributed to the female sex hormone-induced suppression of urinary oxalate excretion and suppression of osteopontin[9] expression in the kidney.

Based on the limited identified data including those on acute doses that induce renal toxicity in humans, the comparative proportions of total metabolites excreted as the putatively toxic entity (i.e., oxalic acid) in humans and rats (Reif, 1950; Frantz *et al.*, 1996a,b) and the specific activity of relevant enzymes in hepatic extracts of rats versus humans, it is expected that the sensitivity of humans to renal effects is similar to or greater than that of rats. Available data indicate that humans may be more sensitive than rodents to the acute toxicity of ethylene glycol, with available information on reported minimum lethal doses being consistent with an approximately 10-fold greater sensitivity in humans compared with rodents. The specific activity of alcohol dehydrogenase (the first rate-limiting step in the metabolism of ethylene glycol, considered essential in producing the toxicological effects associated with exposure to this substance) has been slightly higher in hepatic extracts obtained from humans, compared with rats (Zorzano and Herrera, 1990).

Less is known about the potential mode of induction of developmental effects, including the role of putatively toxic metabolites, although research conducted to date has focused on glycolic acid (Carney, 1994; Carney *et al.*, 1999). This focus has related to both the metabolic acidosis induced by the increased accumulation of this substance in the blood as well as possible toxicological effects of the

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[8] However, in one of these studies (Lee *et al*, 1992), the reported intake of drinking water was slightly lower in the females (18.3 ± 7.2 mL/day) than in the males (25.1 ± 9.3 mL/day).

[9] A glycoprotein that is part of the calcium oxalate crystal matrix, considered to promote the formation of kidney stones (Iguchi *et al*, 1999).

substance itself. On the basis of current data, however, the likely less important role of other metabolites in the induction of developmental effects cannot be excluded.

Evidence implicating a role for glycolic acid as the principal teratogenic agent has been derived from *in vitro* studies of rat embryo cultures, in which developmental changes (e.g., craniofacial dysmorphogenesis), consistent with some effects noted *in vivo*, were observed at concentrations of glycolic acid (i.e., 12.5 mM) less than those for ethylene glycol (i.e., 50 mM) having no effect (Carney, 1996). Similarly, in *in vivo* studies, developmental effects have been observed in rats administered glycolic acid at doses less than those for ethylene glycol inducing similar effects (Munley and Hurrt, 1996; Carney *et al.*, 1999).

In studies in rats, a reduction in the metabolic acidosis typically associated with oral exposure to ethylene glycol ameliorated, but did not completely eliminate, teratogenic effects (Khera, 1991; Carney *et al.*, 1999). Most variations and malformations induced by 2500 mg ethylene glycol/kg-bw administered on days 6–15 of gestation were similar to those observed among fetuses from dams receiving an equivalent "teratogenic dose" of either glycolic acid (presence of metabolic acidosis) or sodium glycolate (absence of metabolic acidosis). However, increased incidence of several external malformations (e.g., meningoencephalocele, exencephaly, omphalocele, cleft lip, cleft palate) among the offspring of ethylene glycol-exposed pregnant rats could not be explained on this basis (Carney *et al.*, 1999).

It has also been suggested that the somewhat disproportionate increase (6.4 for a 3-fold increase in dose) in concentrations of glycolic acid in the blood of pregnant rats administered between 150 and 500 mg ethylene glycol/kg-bw may be important in the induction of developmental effects in this species (Pottenger *et al.*, 1998), although this does not parallel well the doses at which developmental effects begin to be observed in rats.

The greater sensitivity of mice, compared with rats, to the teratogenic effects associated with exposure to ethylene glycol (Neeper-Bradley *et al.*, 1995) has also been postulated to be attributable to the saturation of the metabolism of glycolic acid (to glyoxylic acid) at reportedly lower doses in mice than in rats. However, data presented in the accounts of three relevant studies (Frantz *et al.*, 1996b,c; Pottenger *et al.*, 1998) are inadequate as a basis for consideration of this hypothesis due to the extremely limited information that permits comparison of the proportion of the total dose excreted as glycolic acid at similar time points for a range of comparable doses in the two species.

2.4.4 Humans

There are numerous case reports concerning the accidental or deliberate ingestion of this compound in humans, although available data from these studies are generally inadequate as a basis for quantitation of intake associated with observed effects. Published values for the minimum lethal oral dose in humans have ranged from approximately 0.4 g/kg-bw (RTECS, 1999) to 1.3 g/kg-bw (ATSDR, 1997).[10]

[10] The minimum lethal oral dose in rats is 3.8 g/kg-bw (Clark *et al*, 1979).

Systemic signs of toxicity following ingestion generally progress in three stages, commencing with effects on the central nervous system (intoxication, lethargy, seizures and coma) and metabolic disturbances (acidosis, hyperkalemia, hypocalcemia), progressing to effects on the heart and lungs (tachycardia, hypertension, degenerative changes) and finally renal toxicity (deposition of calcium oxalate, hematuria, necrosis, renal failure) (Kahn and Brotchner, 1950; Freidman *et al.*, 1962; Parry and Wallach, 1974; Siew *et al.*, 1975; Gordon and Hunter, 1982; Cheng *et al.*, 1987; Denning *et al.*, 1988; Spillane *et al.*, 1991). In addition to the immediate central nervous system effects, neurological effects (including facial paralysis, slurred speech, loss of motor skills and impaired vision) have been observed up to several weeks following ingestion, suggestive of cranial nerve damage (Ahmed, 1971; Parry and Wallach, 1974; Mallya *et al.*, 1986; Spillane *et al.*, 1991; Huhn and Rosenberg, 1995). Ethylene glycol may also produce a local irritant effect on the gut and cause pain and bleeding secondary to gastric erosion (Gordon and Hunter, 1982; Spillane *et al.*, 1991). The type and severity of toxicological effects observed following ingestion vary with the amount of ethylene glycol consumed, the interval between ingestion and treatment, and whether there has been concurrent ingestion of ethanol (Robinson and McCoy, 1989).

Information concerning adverse effects following inhalation of ethylene glycol is limited to observational data in a single case report (Hodgman *et al.*, 1997) and the results of one laboratory study in which a range of endpoints (physical examinations, psychological testing, and analysis of hematological, serum clinical chemistry and urinary parameters) was examined in 20 male volunteers exposed (whole body) to ethylene glycol aerosol (Wills *et al.*, 1974). In the latter study, no significant adverse effects were observed among individuals exposed (to up to 67 mg/m^3) continuously for periods up to 30 days, although some individuals experienced throat irritation, headache and back pain. Following a gradual increase in the exposure concentration, nasal and/or throat irritation were noted in all test subjects at 140 mg/m^3 and above, while concentrations above 200 mg ethylene glycol/m^3 produced severe irritation and could not be tolerated (Wills *et al.*, 1974).

Ethylene glycol is a mild ocular irritant in humans. In dermal patch tests, results have been consistently negative in healthy volunteers (Meneghini *et al.*, 1971; Hindson and Ratcliffe, 1975; Seidenari *et al.*, 1990), while dermal irritation has been noted in individuals with dermal sensitivity, including eczema patients (Hannuksela *et al.*, 1975) and occupationally exposed workers with a history of dermatitis (Hindson and Ratcliffe, 1975; Dawson, 1976).

Identified epidemiological studies are restricted to two investigations, the results of which are considered inadequate to assess the carcinogenicity of ethylene glycol in humans. In a cross-sectional survey, there was no evidence of effects on kidney function (based on urinary concentrations of albumin, β-N-acetyl-glucosaminidase, β-2-microglobulin and retinol-binding protein) in a small group of aircraft workers (some of whom wore protective breathing equipment) exposed to ethylene glycol vapour or mist during deicing operations (Gérin *et al.*, 1997). In the single case–control study identified (Bond *et al.*, 1985), there was no association between presumptive inhalation exposure to ethylene glycol (and other chemicals) and renal cancer in chemical production workers. Quantitative data on exposure to ethylene glycol were not presented.

3.0 RISK CHARACTERIZATION

3.1 Environment

3.1.1 General Considerations

Ethylene glycol is used in large volumes in Canada. From available environmental release information, it is the transportation sector, specifically air transportation, that is responsible for the greatest volume of releases of ethylene glycol to the environment and thus has the greatest potential to cause adverse impacts on biota. Releases are attributable to aircraft deicing/anti-icing activities, which occur under cold weather conditions. Through monitoring of airport stormwater effluent, evidence of high levels of ethylene glycol reaching the aquatic environment has been obtained. This has led to recognition and identification of problem areas and encouraged the initiation of remediation efforts and environmentally protective management activities, primarily through Glycol Operational Management Plans (GOMPs) and Glycol Mitigation Plans (GMPs), coordinated through Transport Canada and involving ATAC airport authorities and air carriers. The CEPA Part IV effluent voluntary guideline of 100 mg total glycol/L (Canada Gazette, 1994) is the current target for glycol management at these airports and should be protective against direct toxicity and indirect toxicity (oxygen depletion) (See Appendix C for current approaches to glycol management at Canadian airports.) Despite the mitigation efforts and control measures currently in place at national and many regional airports, exceedances of the 100 mg/L guideline have been occurring. Concentrations of ethylene glycol in effluent streams as high as 4700 mg/L (Jean Lesage International Airport, March 1999) have been recently measured in the vicinity of airport property lines. These and other concentrations are high enough to cause some concern on a local scale.

Based on its high water solubility (miscible), relatively low vapour pressure (7 Pa at 20°C) and low Henry's law constant (5.8×10^{-6} to 6.0×10^{-3} Pa·m^3/mol), ethylene glycol is unlikely to transfer to air or sediment after release to the aquatic environment. As well, release scenarios indicate that the environmental medium associated with the highest potential for exposure is water. Limited data exist for atmospheric and soil concentrations and no data are available for sediment concentrations, although, due to its high water solubility, accumulation of ethylene glycol in soil and sediment is not expected. Studies of soil permeability indicate that there could be a potential for groundwater contamination as a result of release to this medium; however, environmentally relevant groundwater concentrations measured in the vicinity of aircraft deicing operations indicate that recent maximum levels are below levels that may cause adverse effects on biota. Although there is potential for higher groundwater concentrations, the available data indicate that exposure from this source is of less environmental significance than direct releases to surface water. Therefore, direct exposure through the aquatic environment will be the focus of this risk characterization.

As indicated above, the most significant potential source of environmental exposure to ethylene glycol is the release from aircraft deicing/anti-icing operations. Deicing/anti-icing can occur for more than half the year at Canadian airports. Releases are site specific and depend on local climatic conditions,

which can influence effluent and stream flow volume, as well as degradation rates. Deicing activities occur at airports beginning as early as September and can end as late as June, although heaviest use tends to occur from December to April (Transport Canada, 1995, 1996a,b, 1997a, 1998a; GTAA, 1997, 1998, 1999). During mid-winter — i.e., December, January and February — typical river water temperatures are near 0°C across Canada (EMR, 1970; Environment Canada, 1974, 1976a,b) but will vary with water depth. The temperature of 4°C may be more typical of surface water temperatures found in Canada during the months of March, April, October and November, but temperatures can range from near 0°C in early March and November to 12°C in late April and early October (EMR, 1970; Environment Canada, 1974, 1976a,b). It is recognized that the rate of biodegradation of ethylene glycol, and hence the rate at which DO levels decline in the presence of ethylene glycol, is inversely proportional to temperature (Evans and David, 1974; Klecka *et al.*, 1993). It follows that degradation would be lower during mid-winter and higher in the fall and spring. Therefore, in this analysis, a temperature of 4°C is assumed to represent median deicing season temperatures for Canada.

Because of the seasonal nature of exposure, consideration must be given to the impact that cooler fall, winter and spring seasons have on ethylene glycol-exposed organisms. During these cooler times of the year in Canada, metabolism, growth and development are reduced. In general, for aquatic ectothermic invertebrates and vertebrates, such as insects, fish and amphibians, metabolic rates are governed by ambient water temperatures. During fall, winter and spring, water temperatures will be near 0°C, resulting in a low metabolic rate and therefore a lower oxygen requirement for these species (Jorgensen and Johnson, 1989; Davison, 1991; Boutilier *et al.*, 1997; Tattersall and Boutilier, 1997; Morgan and Hinojosa, 1999). With the productivity of the receiving waters declining at these low temperatures and approaching zero as the temperature nears the freezing point (Gordon *et al.*, 1982), some caution is warranted in extrapolating laboratory results to the natural receiving environment. Toxic effects observed at 20°C may not be observed at temperatures near 0°C.

In reaching a conclusion on the environmental risk characterization of ethylene glycol, consideration is given to the environmental conditions at the time of release, the concentrations of ethylene glycol in ambient waters and the frequency of release, in addition to the potential impacts on aquatic life — in particular, impacts on environmental populations. Attention is focused on the direct effects on the most sensitive aquatic species and the indirect effects as a result of biodegradation of ethylene glycol and consequent decline of DO levels.

3.1.2 Environmental risk characterization

3.1.2.1 Aquatic biota — direct effects

Based on the most recent available data from all airports for the 1997/98 and 1998/99 seasons, the levels of ethylene glycol in effluent streams are below 200 mg/L 99% of the time and below 72 mg/L 95% of the time from over 3282 measurements (see Table 4), with the reported maximum of 4700 mg/L measured in the spring of 1999. Although peak use of glycol tends to occur during mid-winter (GTAA, 1999), volumes released can also be high in spring due to an increase in freezing precipitation events,

snowmelt or spring runoff. In addition, the period in spring is significant in terms of potential exposure of breeding species of aquatic vertebrates and invertebrates. The concentrations of ethylene glycol in effluent streams, measured during March and April from all of the airports, for the most recent 1998/99 season were below 90 mg/L 99% of the time; however, a distribution of maximum concentrations at individual airports for these months provides a higher range of values (see Table 7).

Natural dilution of effluents will be occurring in the receiving waters and must be considered in calculating the risk to aquatic organisms. The level of dilution will vary with each location; therefore, a generic and conservative dilution factor of 10 is applied (see Appendix for detailed rationale). The effluent concentrations are assumed to be reduced by 1 order of magnitude — i.e., the isolated maximum effluent concentration of 4700 mg/L becomes 470 mg/L in the receiving waters.

In terms of exposure duration, it is important to note that although daily measurements of ethylene glycol from stormwater effluents are limited, available data indicate that peak concentrations will typically be maintained for a period of 1 or 2 days and subsequently decline to much lower levels (GTAA, 1997, 1998, 1999). Nonetheless, some daily measurements in the past have indicated that higher concentrations can occur for several consecutive days (Aéroports de Montréal, 1997). It will be assumed that under worst-case conditions, high levels of ethylene glycol will be found in the effluent for a period of several days.

3.1.2.1.1 Algae

The green alga, *Selenastrum capricornutum*, was identified as the most sensitive aquatic species to ethylene glycol exposure and was used as the basis for the Canadian Council of Ministers of the Environment (CCME) water quality guideline of 192 mg/L for the protection of aquatic life (CCME, 1997a).[11] As noted above (see Section 2.4.1.1.2), five toxicity tests used the same freshwater algal species, measured cell growth as the toxicity endpoint (Dill *et al.*, 1982; Ward *et al.*, 1992; Aéroports de Montréal and Analex Inc., 1994; Beak Consultants Ltd., 1995b; Pillard and Dufresne, 1999) and followed essentially the same test method (U.S. EPA, 1978, 1989a,b). The lowest IC_{25} was that reported by Aéroports de Montréal and Analex Inc. (1994) at 592 mg/L from one of three experimental trials calculated using a non-parametric linear interpolation statistical model (Norberg-King, 1993), as advised in the test protocol and consistent with the other available studies. For risk characterization, it is appropriate to consider the mean of the three trials, resulting in an IC_{25} of 3268 mg/L. Based on these results, the calculated IC_{25}s are found to range from 3268 to 8825 mg/L. High coefficients of variation and deviations from the test standard protocol — i.e., number of cells/mL, temperature and photoperiod, and expression of test endpoints (Greene Environmental Services, 2000) — make it impossible to average all of the results. As such, only the two studies of Pillard and Dufresne (1999) and Beak Consultants Ltd. (1995b) can be averaged, to provide a mean estimated IC_{25} of 7082 mg/L. Although the study by Aéroports de Montréal and Analex Inc. (1994), which provided the lowest IC_{25} of 3268 mg/L (mean of three experimental trials), cannot be included in the overall mean, it adds to the weight of

[11] The CCME water quality guideline of 192 mg/L was based on the LOEC of 1923 mg/L from two of three experimental trials of equal variance from the Aéroports de Montréal and Analex Inc. (1994) study.

evidence in support of algal sensitivity to ethylene glycol exposure. In this study, the algae were kept in the dark for a period of 8 hours per day; although this would have interrupted the growth, the outcome may be considered to reflect effects expected under more natural conditions. Therefore, the IC_{25} of 3268 mg/L (Aéroports de Montréal and Analex Inc., 1994) is chosen to represent the LOEL.

It is important to note that the three recent studies discussed above (Aéroports de Montréal and Analex Inc., 1994; Beak Consultants Ltd., 1995b; Pillard and Dufresne, 1999) terminated the analysis after 96 hours; however, the studies by Dill *et al.* (1982) and Ward *et al.* (1992) allowed the tests to run for a period of 14 days. These longer studies reported a decrease in the inhibition of growth of *S. capricornutum* after the 96-hour period and at a rate inversely proportional to that of the initial onset of inhibition. Dill *et al.* (1982) reported this for all of the treatment concentrations, and, although the initial cell concentration was an order of magnitude lower in the study by Ward *et al.* (1992), a similar observation was made. It appears that ethylene glycol is primarily inhibiting algal growth during the initial exponential phase occurring within the first 96 hours. By the time 7 days had passed in the Dill *et al.* (1982) study, algal growth (for controls and all concentrations) had reached a level plateau where the number of cells/mL remained essentially constant at $>1.0 \times 10^8$ cells/mL. Such a "recovery" may indicate that, over time, adverse effects on algal populations may be minimal. However, it is not clear if this phenomenon is attributable to *S. capricornutum* only or if it would be observed for all algae and other aquatic plant species. Evidence suggests that it may be a function of the organism rather than the chemical, as similar observations have been made after exposing *S. capricornutum* to other substances, including epichlorohydrin and, to a certain extent, phenol and 4-chlorophenol (Dill *et al.*, 1982), as well as diethylene glycol (Ward *et al.*, 1992); other substances, however, including diethanolamine (Dill *et al.*, 1982) and propylene glycol (Ward *et al.*, 1992), did not induce such a response. Because of this uncertainty, the observed inhibitory effects on *S. capricornutum* during exponential phases of growth will be considered to reflect potential and significant inhibition of growth of other algal species.

It is also significant that for all of the available *S. capricornutum* growth inhibition studies, the tests were conducted at a temperature of approximately 25°C. Given that the primary route of exposure to the environment results from aircraft deicing operations, it would be more appropriate to consider the effects under temperatures more relevant to deicing conditions. Aéroports de Montréal and Analex Inc. (1994) attempted to determine the impact of ethylene glycol on growth of *S. capricornutum* at temperatures of 10 and 4°C but were unable to observe any significant growth at these temperatures, and therefore no toxic effects were measurable. This observation suggests that under cool fall, winter and spring temperatures (<10°C) in receiving waters across Canada, the rate of growth for this species would be minimal. This is supported by the standard practice of storing *S. capricornutum* laboratory cultures at 4°C for extended periods of time — e.g., 6 months or more (U.S. EPA, 1978, 1989a,b). For many temperate algal species, optimum growth conditions occur above 15°C (Reynolds *et al.*, 1975; Lee *et al.*, 1985; Simões Gonçalves *et al.*, 1988; Trainor, 1992; Dehui *et al*, 1998). Other species of algae are adapted to lower temperatures, such as *Chorella vulgaris*, *Synura sphagnicola* and species of diatoms that can have measurable growth at temperatures near 5°C (Wetzel, 1975; Healey, 1983; Maxwell *et al.*, 1994). However, for all algae and other aquatic plants, the rates of growth are significantly reduced at these lower temperatures. Typically, the rate of growth/photosynthesis decreases

by a factor of 2.0 for every 10°C drop in temperature (Q_{10} = 2.0), but the decrease can be much greater as the water temperature approaches 0°C (Davison, 1991).

For this risk characterization, it is assumed that algal species present in receiving waters near Canadian airports will at least be as sensitive as *S. capricornutum* at warmer temperatures. Therefore, using the IC_{25} of 3268 mg/L from the most conservative algae test results (Aéroports de Montréal and Analex Inc., 1994) as the Critical Toxicity Value (CTV) and applying an application factor of 5 to account for interspecies variability and laboratory to field extrapolation, the Estimated No Effect Value (ENEV) of 654 mg/L is obtained. In deriving risk quotients, the Estimate Exposure Value (EEV) is divided by the ENEV (EEV/ENEV), and these are presented in Table 8 for various exposure scenarios.

3.1.2.1.2 Amphibians

As indicated above, spring months can coincide with high levels of ethylene glycol exposure, as well as significant and possibly sensitive events in the life cycle of other freshwater organisms — e.g., invertebrate and amphibian hatching, larval development, breeding, etc. Although data are limited, amphibians appear to be among the more sensitive aquatic animals to ethylene glycol exposure. The only available study that examined the effect of ethylene glycol on amphibians was an acute study on *Xenopus laevis*, a non-native species of clawed frog. The arithmetic mean 48-hour LC_{50} was determined to be 17 509 mg/L from two tests (Beak Consultants Ltd., 1995a). This endpoint falls in the lower range of the acute effects measured for fish species. The 24- to 96-hour LC_{50}s from 10 studies on fish ranged from 17 800 to 83 400 mg/L. From the available subchronic (7- to 14-day) toxicity tests on fish, LOECs and EC_{25}s ranged from 22 520 to 28 333 mg/L for growth. Assuming that the acute to subchronic ratios for fish are similar to those for amphibians, the highest ratio being 3.7, a conservative estimate of the concentration inducing a subchronic effect on amphibians would be 4732 mg/L (17 509 ÷ 3.7). Using 4732 mg/L as a CTV and applying an application factor of 10 to account for the fact that the amphibian study used a non-native species and for uncertainty in laboratory to field extrapolation, the subchronic ENEV becomes 473 mg/L.

Again, for amphibians, consideration must be given to the influence of cold temperatures, which coincide with significant releases of ethylene glycol. During Canadian winters, temperatures drop near or below freezing, and native amphibians typically will enter into a state of dormancy (Bradford, 1984; Tattersall and Boutilier, 1997; Boutilier *et al.*, 1997). During such a state, especially during prolonged periods (several months), the basal metabolism will decrease to 10 or 20% of the normal resting metabolic rate (Boutilier *et al.*, 1997), with the Q_{10} ranging between 2.6 and 6.6 for the common frog (*Rana temporaria*) at temperatures between 5.5 and 1.5°C, respectively (Tattersall and Boutilier, 1997). It follows that where metabolic rates are reduced, toxicity may also be reduced. For example, the toxicity of cadmium was found to be reduced with a decrease in temperature in young tadpoles (Ferrari *et al.*, 1993). In a similar manner, the toxicity of ethylene glycol to native amphibians may also be reduced at these cooler temperatures.

As temperatures warm up in the spring, many Canadian amphibian species will emerge from dormancy (onset of increased metabolic rate) and will often immediately initiate breeding from early April

through May and June, depending on location. The earliest reported date when the first calls of spring peepers (*Hyla crucifer*) were heard was on March 26, 1998, in central Ontario (an earlier than normal date, attributable to the effects of El Niño) (Bishop and Shirose, 1999). In northern Ontario, first calls of the spring peeper have been heard between April 2 and May 2 between 1993 and 1998 (Bishop and Shirose, 1999). Amphibians that emerge in early spring have the potential to be affected by exposure to significant concentrations of ethylene glycol released from airports at this time of year. Because the effects of exposure of amphibians to ethylene glycol under cold temperatures are not available, the conservative ENEV of 473 mg/L for amphibians is compared with the EEV. Various exposure levels (EEVs) are provided in Table 9 for comparison and are used in deriving risk quotients (EEV/ENEV).

3.1.2.1.3 Concluding discussion

Conservative risk quotients are all less than 1.0; however, the conservative risk quotients using the highest reported maximum in the past 2 years are very close to 1.0 (0.99) for amphibians and 0.71 for algae. A more realistic characterization of the potential for adverse population-level effects is considered to be much lower. When estimating the potential environmental risk to a population, the frequency of exposure must be considered. The frequency of these high levels is very low, as only a single effluent concentration from 3282 samples was found to be essentially equivalent to the calculated ENEV for amphibians. In addition, the 99th-percentile concentration from all data from the 1997–1999 seasons is 200 mg/L, which results in an estimated exposure concentration of 20 mg/L, giving a quotient for amphibians 25 times less than 1.0. In addition, under most circumstances, it can be expected that maximum concentrations in releases from airports will not last for more than 1 or 2 days; therefore, one can expect actual high concentrations experienced by aquatic organisms to be of shorter duration than assumed by laboratory tests. Moreover, as discussed above, the ambient temperature can have a significant impact on the physiological rates of activity for algae and other aquatic ectothermic organisms, which will likely lower the toxicity. Furthermore, under current management practices, the concentrations of ethylene glycol being released are expected to continue to decline or be maintained at minimal levels at the 26 major airports under the National Airports System (NAS) in Canada (Aalders, 1999), which handle an estimated 95% of the passenger and cargo volume (Transport Canada, 1999a) and use at least 95% of the ethylene glycol (Leroux, 1999).

3.1.2.2 Aquatic biota — indirect effects

Ethylene glycol is generally rapidly biodegraded in aquatic ecosystems (Sills and Blakeslee, 1992). Biodegradation by a variety of acclimated microorganisms under aerobic or anaerobic conditions is likely the primary removal process for glycols in surface waters. Under some conditions, the biodegradation of glycol can be sufficiently rapid that DO will be depleted in receiving waters (Sills and Blakeslee, 1992), possibly leading to adverse effects on aquatic biota. How quickly biodegradation occurs depends upon a number of factors, including ambient temperature, nutrient levels and the microbial populations in the receiving waters.

In Canada, the CCME has released guidelines for DO levels in water bodies that protect sensitive life stages of warm-water and cold-water aquatic life (CCME, 1999). These Canadian water

quality guidelines are based in part on those derived by the B.C. Ministry of Environment, Lands and Parks (Truelson, 1997) and Alberta Environmental Protection (AEP, 1997). British Columbia has established an instantaneous minimum criterion of 9 mg/L for early sediment-dwelling life stages of aquatic organisms and a 30-day mean of 11 mg/L for the same species (Truelson, 1997). In Alberta, DO guidelines for surface water are set at 8.3 mg/L for a 7-day mean from mid-May to the end of June to protect the emergence of mayfly species and 9.5 mg/L for early life stages in the sediment. These and other invertebrate species are important food for other organisms, and juvenile forms will overwinter in the sediment layers before emergence in the spring in many small Canadian rivers and streams (Barton and Taylor, 1996; AEP, 1997; Beak International Inc., 1997; House of Hiking and Fishing, 1999). The Alberta government's 1-day minimum to be met at all times is set at 5 mg/L (AEP, 1997). The Canadian water quality guidelines have been derived for DO for the protection of freshwater aquatic life and can be seen in Table 10 (CCME, 1999).

The DO requirements of fish vary with season, health and life stage. The DO cold-water guideline applies to waters that support cold-water fish species, including salmonids, smelts, pikes, sculpins, walleye and smallmouth bass. Where no such fish species are present, the warm-water guidelines apply (CCREM, 1987). For many streams and water systems that receive stormwater effluent from airport facilities, there may be no natural cold-water fish species, although these species are recognized to exist in every province or territory in Canada (DFO, 1995). In the case where the natural background concentration is less than 110% of the guideline value for early life stages of cold-water fish (e.g., <10.45 mg/L), the minimum acceptable concentration becomes 90% of the natural upstream concentration of DO (CCME, 1999).

Although most species of fish, amphibians and invertebrates will overwinter in a more mature state, some can or will overwinter in the more juvenile stages, including the mountain whitefish (*Prosopium williamsoni*), bull trout (*Salvelinus confluentus*) and burbot (*Lota lota*) (Chambers and Mill, 1996), some invertebrates (Markarian, 1980), including the common mayfly, *Baetis tricaudata* (Lowell and Culp, 1996), and some amphibians, including the green frog (*Rana clamitans*) and the spotted frog (*R. pretiosa*) (Industry Canada, 1999). The juvenile species tend to be more sensitive to the effects from exposure to ethylene glycol (CCME, 1999) and may be exposed during winter deicing operations. As noted above, the metabolic rate and thus the normal consumptive demands of ectothermic aquatic biota such as fish, amphibians and invertebrates are lessened at cooler temperatures. For example, the oxygen consumption for goldfish (*Carassius auratus*) exposed to water at 5°C was 17.5-fold lower than at 25°C (Fry and Hart, 1948).

In order to predict the impact of ethylene glycol on the DO level of ambient waters following aircraft deicing operations, the Streeter-Phelps oxygen sag model has been used. The Streeter-Phelps oxygen sag model was initially developed to predict water quality downstream of wastewater discharges (Streeter and Phelps, 1925). The model assumes that the discharge has a constant flow, constant BOD, rapid and complete lateral mixing of the discharge in receiving water, and that effects of photosynthesis and benthic processes are negligible. The application of the Streeter-Phelps model for estimating the effects from ethylene glycol discharge from aircraft deicing operations does not completely conform with the assumptions under which the model was derived; however, it is considered adequate for the following

reasons. It is recognized that all discharges will not be constant in flow or composition, and typically discharge concentrations will peak in the first day or two of release, followed by subsequent decline (GTAA, 1997, 1998, 1999). However, for the purposes of the model, concentrations are considered stable enough to allow the model to estimate the DO levels with reasonable accuracy (Parker, 1999b). Also, deicing and anti-icing fluids are applied periodically during fall, winter and spring months in conjunction with cold-weather precipitation events, which can continue for several days. Applied ethylene glycol may be entrained in runoff water from the precipitation event or may be incorporated in the nearby snow, followed by subsequent release during spring melt (Corsi *et al.*, 1999). Surface water discharge under these conditions can last for a period of days, long enough for adequate application of the model. The more typical variation in concentration with time will cause some longitudinal diffusion and mixing in the receiving water; therefore, it is expected that the maximum in-stream concentrations associated with a given deicing event will be somewhat reduced during downstream transport (Corsi *et al.*, 1999). Therefore, by assuming that the maximum in-stream concentration is not reduced during downstream transport (except by degradation), the model will tend to overestimate the actual oxygen deficit (Parker, 1999b).

The Streeter-Phelps model also assumes that the discharge is rapidly mixed laterally in the stream and hence represents the stream as a one-dimensional system. This assumption will be valid in streams that are fast moving and have substantial turbulence. In slow-moving streams, the assumption of rapid lateral mixing may not be appropriate, and a local mixing zone, with elevated BOD concentrations and increased oxygen deficits, may be present. Given that ethylene glycol discharges will occur during runoff or precipitation events, which tend to correspond to increased stream flows, it is likely that most of the streams of concern could be considered as having sufficient lateral mixing to minimize the impact of increased localized concentrations (Parker, 1999b).

Below is the Streeter-Phelps model (Streeter and Phelps, 1925):

$$D = \underbrace{\frac{k_1 L_0}{k_2 - k_1}\left[e^{-k_1 t} - e^{-k_2 t}\right]}_{\text{Oxygen deficit as a result of loading.}} + \underbrace{D_0 e^{-k_2 t}}_{\text{Initial oxygen deficit from saturation.}}$$

where:

- D = DO deficit (from saturation) (mg/L),
- t = travel time in stream from discharge location to point of interest (days),
- k_1 = rate constant for BOD decay (day^{-1}),
- k_2 = re-aeration rate constant (day^{-1}),
- L_0 = initial BOD immediately downstream of the discharge (mg/L), and
- D_0 = DO deficit immediately upstream of the discharge (mg/L).

The model can determine the critical time t downstream at which point the DO is at a minimum and the rate of re-aeration equals the rate of oxygen consumption. It will be assumed that downstream transport will continue for a period of 3 days, since most streams or creeks will receive water from

another tributary or flow into a larger system within a period of 3 days (Corsi *et al.*, 1999; Parker, 1999b), and hence the oxygen level of the water will likely increase and the concentration of ethylene glycol will be reduced.

Only one reliable study was available for which the decay rate constant (k_1) was determined under winter-relevant conditions. The k_1 of 0.033 day^{-1} was determined following standard test protocol at an ethylene glycol concentration of 50 mg/L and using ample acclimated soil bacteria at a temperature of 4°C (Williams, 1995). Propylene glycol rate constants also fall in the same range — i.e., at 12°C between 0.06 and 0.17 day^{-1} at propylene glycol concentrations of 1000 and 100 mg/L, respectively. Similarly, the rate constants for propylene glycol at 4°C were 0.05 and 0.07 day^{-1} at concentrations of 1000 and 100 mg/L, respectively (Camp Dresser and McKee, 1997). These values increase confidence in the rate constant, which is critical to the calculations. It is important to note that both low nutrient availability and limited acclimated bacterial populations may reduce the rate at which the ethylene glycol is degraded in the ambient environment. Therefore, in some streams, the Streeter-Phelps model may overpredict oxygen deficits due to limited availability of nutrients or acclimated biomass.

Natural levels of DO in Canadian surface waters can and do vary considerably with location, atmospheric and hydrostatic pressures, water depth, turbulence and velocity, temperature, salinity, groundwater recharge, ice cover, photosynthetic activity, respiration, biodegradation and characteristics of the watershed (Wetzel, 1975). Generally, variations in oxygen levels are not the result of point source discharges (CCME, 1999). Data on DO levels in rivers across Canada are limited. The NAQUADAT 1985 database indicates that DO levels in surface waters (some of which are likely influenced by anthropogenic sources) range from non-detectable to 18.4 mg/L (n = 12 076) (CCREM, 1987; CCME, 1999). In a survey of upstream concentrations in Truro Creek, outside Winnipeg International Airport, concentrations ranged between 2.3 and 12.1 mg/L, with means of 8.4 and 7.6 mg/L, from April to June in 1997 and 1998, respectively (North/South Consultants Inc., 1998). Upstream and downstream of Toronto's Lester B. Pearson airport, concentrations ranged from 11 to 12.7 mg O_2/L during October 1996 and March 1997, with the highest levels reported in March (Beak International Inc., 1997). In a survey of ice-covered Canadian rivers under the Northern River Basins Study, carried out by Environment Canada and Alberta Environmental Protection, concentrations ranged from 0.96 to 14.1 mg O_2/L (mean = 9.16 mg/L, n = 381) (Chambers and Mill, 1996; Chambers *et al.*, 1996, 1997). One seasonal factor that can influence the level of DO is the ambient temperature, because cold water has a higher absorptive capacity for oxygen than warm water. At 101.3 kPa and 20°C, the saturation point for DO in water is 9.08 mg O_2/L, whereas at 4°C it is 13.1 mg O_2/L (Tchobanoglous and Burton, 1990).

Although the initial DO level in surface waters can vary to a great degree and empirical data are limited, for this analysis it is assumed that under cold winter conditions, the initial DO level has reached about 95% of saturation (i.e., 12.4 mg/L). This assumption is considered to be justified, since elevated ethylene glycol discharges are most likely during rainfall and snowmelt events, and hence the receiving waters should have elevated flows. This will create conditions that favour re-aeration and hence elevated initial DO concentrations (Parker, 1999b).

Under natural winter conditions, the restriction of oxygen exchange due to ice cover can cause significant depletion of DO (CCME, 1999). Notably, under conditions of ice cover, which will occur in receiving waters near airports, decomposition of the organic matter in the stream over the winter can lead to a gradual decline in the DO level. Input of ethylene glycol into ice-covered receiving waters adds to the BOD and can further deplete the DO level of the stream. A gradual decline in the DO level under ice was observed in the high-volume Athabasca River system, where inputs of high BOD from pulp and paper and municipal effluent caused a decline of DO from 12 to 7.2 mg/L over a distance of 450 km (Chambers *et al.*, 1996).

For characterization of risk from indirect effects, the input parameters applied to the Streeter-Phelps model include the assumption of complete ice cover and therefore no re-aeration, a dilution factor of 10, an initial DO concentration of 12.4 mg/L and concentrations of ethylene glycol in stormwater (maximums and percentiles) released from 32 airports during the 1997/98 and 1998/99 seasons. Oxygen deficit quotients are provided in Table 11.

From the quotients presented in Table 11, it is apparent that depletion of oxygen below the CCME guideline of 9.5 mg/L is not expected to occur at releases of 200 mg/L and at the CEPA Part IV guideline of 100 mg/L; however, the potential for significant oxygen depletion appears to exist when the analysis assumes the worst-case maximum levels. Results of a separate probabilistic modelling study that used maximum loadings from individual airport facilities during the 1997/98 or 1998/99 season and assumed complete ice cover predicted DO levels below the CCME DO guideline to occur about 17% of the time under worst-case conditions (Parker, 1999a). It is important to recognize that loadings of ethylene glycol at these high levels are rare (see Figure 2 and Table 4) and that consideration must be given to the fact that these predictions are based on many conservative assumptions — i.e., no re-aeration, instantaneous mixing, use of one-time maximum effluent concentrations, DO requirements of aquatic organisms are not reduced in winter, travel time in the receiving waters before being re-aerated in the stream is set at 3 days, dilution is assumed to be a factor of 10, etc. In addition, the guideline value of 9.5 mg/L is specifically applicable to cold-water fish species, which may not be present in the receiving waters during the time of deicing. Application of the warm-water guideline would substantially reduce the levels of adverse effects from a decline in DO. Also, the degradation rate constant used in all of the scenarios is based on a 5-day BOD test using acclimated soil bacteria in a nutrient medium at 4° C. It can therefore be expected that degradation would likely occur at a lower rate in the natural environment where nutrients and biota may not be as abundant and biota may not be as acclimated to ethylene glycol. Moreover, the theoretical oxygen demand of 1.29 mg O_2/mg ethylene glycol is assumed, which may tend to overestimate the actual amounts of DO consumed, as empirical data would suggest that lower levels of consumption are more likely (see Section 2.4.1.2) and biodegradation studies indicate that the BOD may be 69–81% of the theoretical oxygen demand (Urano and Kato, 1986).

3.1.2.3 Uncertainty and recommendations

3.1.2.3.1 Direct effects

There are numerous sources of uncertainty in this risk characterization. In particular, there is a notable lack of measurements of ethylene glycol in the ambient environment. However, a large data set of measurements of ethylene glycol in effluent concentrations from Canadian airports provides a very good indication of quantities being released. Because the conditions of the receiving waters can be highly variable across Canada, some conservative assumptions, including use of a dilution factor of 10, have been applied. By doing this, it is expected that an adequate estimate of the concentrations of ethylene glycol in the receiving waters can be obtained.

The use of deicers and anti-icers at airports across Canada will vary from year to year and from region to region, depending on climatic factors; however, it is important to note that data from several years from a sampling of the major airports in Canada have been considered in this characterization and are assumed to capture a variety of weather conditions, including the 1998 ice storm in eastern Ontario and western Quebec. It is also apparent that the development and implementation of GMPs at the airports will also vary markedly from airport to airport; however, the 32 airports for which data were available use the vast majority (>95%) of ethylene glycol across Canada. Available evidence suggests that as a direct result of control efforts by Transport Canada, ATAC, local airports and airlines and the implementation of GMPs and GOMPs at the major airports in Canada, the levels of ethylene glycol being released to the ambient environment have been declining over the past years.

Another area of uncertainty is in the reported formation of oxalate crystals in the kidneys of fish chronically exposed to ethylene glycol-based deicing fluid (Evans, 1990; Hartwell *et al.*, 1993, 1995). Hartwell *et al.* (1993) suggested that the chronic effects of deicing operations using ethylene glycol-based deicers may be long-lasting and could result in permanent debilitation. Although the presence of oxalate crystals in the kidneys and the other effects in the Hartwell et al. (1995) study are said to occur as a result of exposure to aircraft deicing fluid, it is acknowledged that they are very likely the direct result of the presence of large quantities of ethylene glycol in the effluent. The metabolic relationship between oxalate crystals and ethylene glycol is clear (Carney, 1994), and the results were consistent with those observed in the kidney of mammals (see Sections 2.4.1.1.6, 2.4.3.3 and 2.4.3.4); however, the results of the Hartwell *et al.* (1993, 1995) and Evans (1990) studies are difficult to interpret due to the presence of the formulated product rather than ethylene glycol alone. In addition, the Hartwell *et al.* (1995) study did not establish a dose–response relationship, making interpretation of cause and effect difficult, and the effects were essentially histological, making it difficult to extrapolate to adverse population-level effects.

Another area of uncertainty involves the fact that fish increase their respiration rate in order to compensate for low DO (an indirect effect), a response that can mean greater exposure to potentially harmful substances as flow rate across gill tissue increases. In addition, aircraft deicing/anti-icing fluids are composed of numerous ingredients, including surfactants, rust inhibitors, thickeners, etc. These components of the formulation, as well as other chemicals that may be present in the effluent, such as

petroleum products, may be more toxic than the ethylene glycol and may make the organisms more susceptible to adverse effects from exposure to ethylene glycol. These other substances present in the effluent stream can also contribute to increased direct toxicity and/or to a reduction in available oxygen in the water body through additional biodegradation. Although these factors were not directly addressed in this characterization, the potential for combined effects of this nature can, to some extent, be captured by dividing the lowest measurement endpoint concentrations (CTV) by an application factor.

3.1.2.3.2 Indirect effects

The assumptions of the Streeter-Phelps oxygen sag model may not be perfectly applicable to the intermittent-release scenario from aircraft deicing operations, and its application is recognized to be better suited to a site-specific model, where effluents are continuous and the receiving waters are well characterized (e.g., temperature, DO content, organic carbon content), as was the intent of the authors (Streeter and Phelps, 1925). However, most assumptions regarding model input parameters used in this analysis were conservative, and natural conditions may not result in the induction of adverse effects. It is also understood that many receiving water bodies will not have "upstream" DO levels that are above the CCME water quality guideline of 9.5 mg/L. Many reported levels of DO are, in fact, below the target guideline; therefore, any input of ethylene glycol to receiving waters in this state will further reduce the level of oxygen below critical levels. This may be especially significant under ice-covered conditions, where opportunity for re-aeration may be negligible. It is apparent, however, that many of the receiving waters around airports are not home to cold-water fish species; as a result, the warm-water guideline (6.0 mg/L) would be applicable. Under a similar analysis as provided above, using the warm-water guideline, the likelihood of adverse impacts would be substantially reduced.

Based on the present analyses, it would seem that harmful environmental effects are unlikely to result from exposure to ethylene glycol in Canada. However, effects related to depletion of DO levels in receiving waters may be possible near some Canadian airports a very small percentage of the time under conditions of maximum loading. It is therefore recommended that current efforts to reduce releases of ethylene glycol during aircraft deicing/anti-icing operations continue to be strengthened, with the aim of reducing further the instances when ethylene glycol concentrations in stormwaters exceed the CEPA Part IV guideline of 100 mg total glycol/L.

3.2 Environment upon which life depends

Since the estimated atmospheric (tropospheric) lifetime for ethylene glycol is too short for transport to the stratosphere and as ethylene glycol contains no chlorine atoms, ethylene glycol does not contribute to the depletion of the ozone layer. Its POCP is low, and its GWP is negligible.

3.3 Human health

3.3.1 Estimated population exposure

Data on levels of ethylene glycol in environmental media in Canada to serve as a basis for development of estimates of population exposure were identified only for areas near industrial point sources in Alberta. These data are limited to a few predicted concentrations in ambient air at ground level and to measured concentrations in soil. No data were identified concerning the presence or concentrations of ethylene glycol in drinking water in Canada or elsewhere.

Very meaningful deterministic estimates of average exposure for the general population are precluded due to the limitations of the available data. Worst-case intakes have been estimated for populations near industrial point sources of ethylene glycol, although the limitations of the available data, which serve as the basis for these upper-bound estimates, must be borne in mind in their interpretation. On this basis, intake is estimated to range from 22 to 88 μg/kg-bw per day, as summarized in Table 12.

Data on levels of ethylene glycol in food are limited to results of two earlier studies of migration from RCF and PETE bottles in other countries and to reported concentrations in Italian wines. Worst-case intakes from ingestion of foods assumed to be contaminated with ethylene glycol through contact with food packaging materials have been estimated for the general population. On this basis, intake is estimated to range from less than 2.5 to 41.0 μg/kg-bw per day, as summarized in Table 13. Migration to food from RCF accounts for most of the estimated intakes.

Based on available data, the general population may be exposed periodically to ethylene glycol through the use of several consumer products, including for example, automobile antifreeze, wax, polish and windshield washer solution, floor wax and polish, tub and tile cleaner and latex paint. Estimation of exposure from such products is incomplete, due to the lack of adequate data on the proportions which include ethylene glycol as an ingredient and on the concentrations in the various products available. Although automobile coolant (i.e., antifreeze) and winter windshield washer fluid are expected to contain the highest concentrations of ethylene glycol, human exposure to these products is expected to be infrequent and of short duration for a small number of individuals and negligible for the majority of the general population. Also, while some inhalation exposure is expected during use of the products mentioned above, intakes by inhalation were not estimated, since the physical-chemical properties of ethylene glycol limit its rate of evaporation from liquid products and the application of these products do not generally involve formation of aerosols.

Intakes by dermal absorption have been estimated for adults using these consumer products (Health Canada, 2000). Generic estimates of the maximum concentrations of ethylene glycol in these products are assumed, as data from analyses of specific products in Canada are not available for this purpose. Based on the worst-case assumptions of 100% dermal absorption of ethylene glycol from thin films of liquid products containing the maximum expected concentrations of ethylene glycol, in standardized scenarios using estimates of frequencies of use and areas of exposed skin, the upper-bounding estimates of daily intakes by adults range from 0.09 to 236 μg/kg-bw per day for the four

product types for which generic estimates of ethylene glycol content are available. This information is summarized in Table 6.

The highest estimates of daily intake by adults due to dermal absorption of ethylene glycol from consumer products result from the standardized scenarios involving the use of tub and tile cleaner. Although mid-point estimates of event frequencies are assumed (i.e., 156 and 48 events per year), these frequencies are considerably higher than the conservative estimates of event frequencies assumed in the scenarios involving the three other consumer product types in Table 6. Therefore, daily intakes are higher for the tub and tile cleaner, even though higher concentrations of ethylene glycol may be present in the other product types.

It should be noted that these values represent worst-case estimates. Estimated daily intakes by dermal absorption of ethylene glycol from use of these consumer products are several orders of magnitude less when based on less conservative assumptions. These include the assumptions that dermal absorption is proportional to the concentration of ethylene glycol in the products and that steady-state penetration occurs for periods equivalent to the average durations of product uses in the standardized scenarios (Health Canada, 2000). However, available data on permeability through human skin are inadequate as a basis for confident estimation of exposure, and, as a result, these estimates are not presented here. This is due to lack of evidence of adequate viability of the skin in the most comprehensive investigation conducted to date, i.e., that by Sun *et al.* (1995), which may have been compromised due to use of samples of full thickness and lack of identified data on uptake from product formulations (Moody, 1999; Health Canada, 2000).

A proportion of the population is also exposed to ethylene glycol as passengers during deicing operations for aircraft. While the pattern of exposure of individuals in the population is expected to be highly variable, depending upon frequency of airline travel during the winter season, identified data are inadequate to quantitatively estimate intake from this source.

3.3.2 Hazard characterization

There is convincing evidence that the toxicity of ethylene glycol is mediated principally through metabolites. Available data indicate also that the likely pathways involved in the metabolism of ethylene glycol are qualitatively similar in humans and other mammalian species; potential quantitative differences have not been well studied.

3.3.2.1 Carcinogenicity

Identified data in humans are inadequate as a basis for assessment of the weight of evidence for causality of the potential carcinogenicity of ethylene glycol, being limited to the results of a single case–control study of chemical production workers, in which there was no association between presumptive exposure to ethylene glycol and renal cancer (Bond *et al.*, 1985). Ethylene glycol has not been carcinogenic in a 2-year bioassay in rats for which sensitivity was somewhat compromised at the top dose in males due to high mortality (DePass *et al.*, 1986a) or in a comprehensive bioassay in mice

(NTP, 1993) exposed in the diet, nor in early (more limited) dietary studies in rats (Morris *et al.*, 1942; Blood, 1965) or monkeys (Blood *et al.*, 1962). In the limited number of identified *in vitro* and *in vivo* studies, ethylene glycol has not been genotoxic.

3.3.2.2 Non-neoplastic effects

Ethylene glycol has low acute toxicity in experimental animals following oral, inhalation, or dermal exposure. Based upon comparison of published values for the minimum lethal dose in humans [ranging from approximately 0.4 g/kg bw (RTECS, 1999) to 1.3 g/kg bw (ATSDR, 1997)] and rats [3.8 g/kg bw (Clark et al., 1979)], humans may be more sensitive to the lethal effects of acute ethylene glycol poisoning than experimental animals, though due to limitations of quantification of exposure in poisoning cases, these conclusions should be cautiously interpreted.

In both humans and animals, ethylene glycol has induced only minimal dermal irritation. Nasal and/or throat irritation were reported in a small number of subjects inhaling ethylene glycol, while higher concentrations produced severe irritation (Wills *et al.*, 1974). In experimental animals, ethylene glycol induces only minimal conjunctival irritation, without permanent corneal damage. Data on the potential of ethylene glycol to induce sensitization have not been identified.

Though there was no evidence of effects on renal function in a small group of aircraft workers (some of whom wore protective breathing equipment) exposed in a cross-sectional survey to ethylene glycol vapour or mist during de-icing operations (Gerin et al., 1997), available data from acute poisoning cases (humans) and repeated dose toxicity studies (experimental animals) indicate that the kidney is a critical organ for the toxicity of ethylene glycol in both humans and experimental animals. Data in humans are inadequate for quantitation of doses which result in renal effects (deposition of calcium oxalate, haematuria, necrosis, renal failure). However, in experimental animals, though also observed in female rats, and males and females of other species in short-term, subchronic, and chronic oral studies, the male rat has been most sensitive in the development of degenerative changes in the kidney associated with ethylene glycol (calcium oxalate crystalluria and calcium oxalate nephrosis). Available data are consistent with the metabolism of ethylene glycol to oxalic acid and the subsequent formation and deposition of calcium oxalate crystals being important requisite steps in the induction of these renal lesions, though, a potential role of other metabolites cannot be completely excluded. In their most severe form, these lesions are incompatible with life (and responsible for most of the deaths in human poisonings by ethylene glycol).

In rodents, mild liver damage (including fatty degeneration, hyaline degeneration, bile duct proliferation, diffuse or centrilobular atrophy) has also been observed at doses higher than those associated with the induction of effects in the kidney of male rats in longer-term studies.

Effects of ethylene glycol on other systems (including the blood, lung and heart) have not been consistently observed at lowest doses.

Based on a rather extensive database, ethylene glycol induces developmental effects in rats and mice by all routes of exposure, although at doses greater than those associated with renal effects in male rats. Indeed, ethylene glycol is teratogenic, inducing primarily skeletal variations and malformations, sometimes at doses less than those that are maternally toxic, with mice being more sensitive than rats. Although most research has focused on the possible role of glycolic acid and/or associated metabolic acidosis in the induction of developmental effects by ethylene glycol, a possible role for other metabolites and/or ethylene glycol itself cannot be excluded on the basis of available data.

The reproductive toxicity of ethylene glycol has been extensively investigated in adequate studies in mice and rats. In repeated-dose toxicity studies, there has been no evidence of adverse impact on reproductive organs; in specialized studies, including a three-generation study in rats and continuous-breeding protocols in mice, evidence of reproductive effects has been restricted to mice (but not rats or rabbits) exposed to doses considerably greater than those associated with developmental effects in this species or renal effects in rats.

Available data are inadequate to assess potential adverse neurological or immunological effects associated with long-term exposure to ethylene glycol, although neurobehavioural and neurological disorders have been reported in cases of acute ethylene glycol poisoning in humans. In the limited number of investigations identified to date, neurological effects have not been observed at doses below those that have induced renal toxicity. Consistent treatment-related effects on immune system-related parameters have not been observed in available repeated-dose toxicity studies, in which several species have been exposed to ethylene glycol either orally or by inhalation.

3.3.3 Exposure–response analysis

Data on exposure–response in humans are limited. They include acute poisoning cases in which exposure has not been well quantified. A short-term study in which a range of endpoints (physical examinations, psychological testing and analyses of hematological, serum clinical chemistry and urinary parameters) has been examined in a small number of human volunteers exposed by whole-body inhalation continuously for periods up to 30 days has also been conducted (Wills *et al.*, 1974). Although inadequate as a basis for characterization of exposure–response, available data in humans are at least somewhat helpful as a basis for crudely characterizing potential relative sensitivity of experimental animals and humans. Exposure–response has therefore been characterized primarily on the basis of results in studies in experimental animals, but including comparison of relative sensitivity with humans where permitted by available data.

It is histopathological effects on the kidney that have typically been observed at lowest doses in laboratory animals exposed to ethylene glycol in repeated-dose toxicity studies in rats, mice and monkeys. Based on subchronic and chronic studies by the oral route in rats and mice (Gaunt *et al.*, 1974; Melnick, 1984; DePass *et al.*, 1986a; Robinson *et al.*, 1990; NTP, 1993), male rats have been the most sensitive sex and species, with data being consistent with the deposition of calcium oxalate crystals within the renal tissue being a requisite step.

Developmental effects (i.e., skeletal changes and, at higher doses, malformations in the absence of maternal toxicity) have also been observed at lowest doses in mice (No-Observed-Effect Level [NOEL] = 150 mg/kg-bw per day[12]; No-Observed-Adverse-Effect Level [NOAEL] = 500 mg/kg-bw per day[13]) and rats (NOAEL = 500 mg/kg-bw per day) administered ethylene glycol orally during gestation (Neeper-Bradley *et al.*, 1995). Effect levels for slight reproductive effects and developmental toxicity in mice in continuous-breeding studies in which ethylene glycol was administered in drinking water were higher (skeletal malformations and slight reproductive effects at 1640 mg/kg-bw per day) (Lamb *et al.*, 1985; Morrissey *et al.*, 1989).

Emphasis in the following sections is on characterization of exposure–response for the endpoint observed at lowest doses in laboratory animals — i.e., renal effects. Developmental effects, which generally occur at somewhat higher concentrations, are also addressed.

3.3.3.1 Oral exposure

The most informative data set for characterization of exposure–response for renal lesions in the most sensitive sex and species (i.e., male rats) is that from the study of Gaunt *et al.* (1974). In this investigation, there were four dose levels of 35, 71, 180 or 715 mg/kg-bw per day, including two at which there was a significant increase of ethylene glycol-related tubular damage. Compared with other relevant studies (Melnick, 1984; DePass *et al.*, 1986a; Robinson *et al.*, 1990), the protocol of this investigation included larger numbers of doses in the lower dose range in the vicinity of reported no-effect levels (i.e., 200 mg/kg-bw per day) and optimum dose spacing (2- to 3-fold compared with 5-fold in longer-term studies). Incidences of both individual lesions and total animals with tubular damage were also reported.

While in the investigation by Gaunt et al. (1974), group sizes were relatively small (n=15) and exposures less than long term (16 weeks), data from the most recent chronic bioassay in larger groups of animals (Depass et al., 1986a) are not considered adequate as a basis for characterization of dose-response for several reasons. Histological reporting of non-cancer lesions in this study was inadequate due to lack of application of consistent diagnostic criteria to assess the onset and progression of treatment-related changes[14]. Moreover, in this chronic bioassay in which there were three dose levels, after 18 months on study, all males in the high dose group had either died or were sacrificed when moribund. Also, the incidence of lesions was almost 100% in the top dose group (1000 mg/kg bw/day) and minimal at the intermediate dose (200 mg/kg bw/day).

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[12] Based upon a statistically significant increase in the incidence of 1 of 27 skeletal malformations/variations (i.e., extra 14th rib on first lumbar arch) at the next highest dose of 500 mg/kg-bw per day.

[13] Based upon a statistically significant increase in the incidence of 25 of 27 skeletal malformations/variations at the next highest dose of 1500 mg/kg-bw per day.

[14] Based in part on information presented in Maronpot (2000a) and Ohanian (2000).

A Tolerable Intake for ethylene glycol, based on the development of histopathological changes in the kidney of male rats, has been derived based on a Benchmark $Dose_{05}$ (i.e., the dose estimated to cause a 5% increase in incidence over the background response rate; BMD_{05}), divided by an uncertainty factor. The BMD_{05} was calculated by first fitting the following model to the dose–response data (Howe, 1995):

$$P(d) = q_0 + (1 - q_0)\left[\ 1 - e^{-q_1 d - \ldots - q_k d^k}\ \right]$$

where d is dose, k is the number of dose groups in the study, $P(d)$ is the probability of the animal developing the effect at dose d and $q_i > 0$, $i = 1,\ldots,k$ are parameters to be estimated.

The models were fit to the incidence data using THRESH (Howe, 1995), and the BMD_{05}s were calculated as the dose D for extra risk that satisfies

$$\frac{P(D) - P(0)}{1 - P(0)} = 0.05$$

A chi-square lack of fit test was performed for each of the model fits. The degrees of freedom for this test are equal to k minus the number of q_i's whose estimates are non-zero. A p-value less than 0.05 indicates a significant lack of fit. For none of the models was there significant lack of fit.

The BMD_{05}s, associated lower 95% confidence limits (95% LCLs) as well as information on goodness of fit for histopathological changes in the kidneys of male rats ingesting diets containing ethylene glycol for 16 weeks (Gaunt *et al.*, 1974) are presented in Table 15. The BMD_{05}s range from 84 mg/kg-bw per day (95% LCL = 45 mg/kg-bw per day) to 550 mg/kg-bw per day (95% LCL = 180 mg/kg-bw per day) for individual lesions (Figure 3). Based on total animals with tubular damage, the respective BMD_{05} and 95% LCL are 49 mg/kg-bw per day and 22 mg/kg-bw per day (Figure 4). Based on these values, a Tolerable Intake has been derived as follows:

$$\text{Tolerable Intake} = \frac{49 \text{ mg/kg-bw per day}}{1000}$$

$$= 0.05 \text{ mg/kg-bw per day}$$

where:

- 49 mg/kg-bw per day is the BMD_{05} calculated based upon total animals with tubular damage in the kidney[15] in the study (16 weeks) in which dose–response was best characterized (Gaunt *et al.*, 1974).

[15] Considered the most appropriate indicator of ethylene glycol-associated renal damage (Wolf, 2000).

- 1000 is the uncertainty factor (x10 for interspecies variation, x10 for intraspecies variation, x10 to account for less than chronic exposure). Available data are inadequate to further address toxicokinetic and toxicodynamic aspects of components of uncertainty with data-derived values. Though the putatively toxic metabolite in induction of renal lesions in rats and humans is likely oxalic acid, the role of other metabolites cannot be completely excluded; moreover there are no comparative kinetic or dynamic data in rats and humans to serve as a basis for reliable quantitative scaling. Limited identified relevant data include that on doses which induce acute toxicity in humans (often not well documented) and rats, the exceedingly limited data (particularly for humans) on comparative proportions of total metabolites excreted as the putatively toxic entity (i.e., oxalic acid) in humans and rats (Reif, 1950; Frantz et al., 1996a,b) and the specific activity of relevant enzymes in hepatic extracts of rats versus humans. Based on this limited information, it is expected that the sensitivity of humans to renal effects is similar to or greater than that of rats; indeed; data for acute poisonings are consistent with the magnitude of this greater sensitivity of humans being in the range of 10 fold, though the limitations of characterization of exposure in human poisoning cases need to be recognized. The specific activity of alcohol dehydrogenase (the first rate limiting step in the metabolism of ethylene glycol (considered essential in producing the toxicological effects associated with exposure to this substance), has been slightly higher in hepatic extracts obtained from humans, compared to rats (Zorzano and Herrera, 1990). The additional factor of 10 to account for less than chronic exposure is necessitated, due to lack of reliable available data to serve as a basis for quantitation of dose-response following long term exposure, likely progression of the effects with continued exposure and decrease in renal function with age.

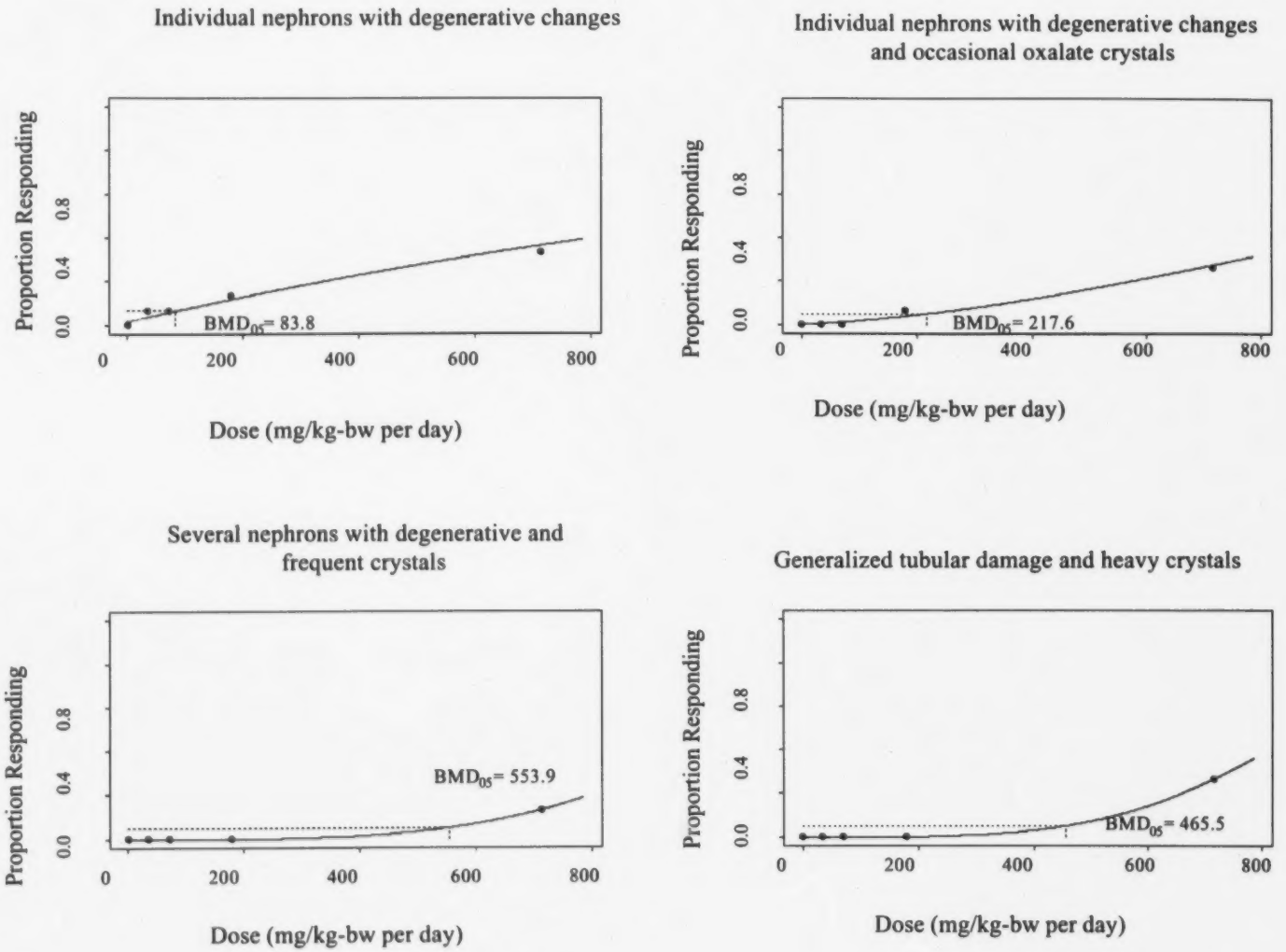

Figure 3. BMD_{05}s based on various renal lesions in male rats

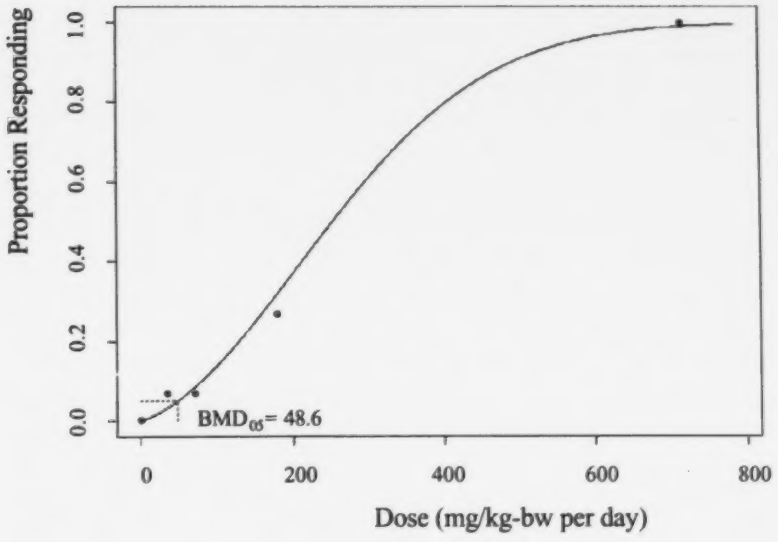

Figure 4. BMD_{05}s based on total animals with tubular damage

For comparison for the sake primarily of completeness, although far less preferred due to poorer characterization of dose–response in the range of interest, BMD_{05}s for renal lesions for which there was increasing incidence with dose have also been calculated (see Table 16) for the only other relevant subchronic study (Robinson *et al.*, 1990).

Tolerable Intakes developed on the basis of histopathological changes within the kidneys of male rats receiving ethylene glycol are expected to be protective for potential developmental effects. Owing to the lack of reported information on litter-specific developmental effects observed at the lowest doses in mice (Neeper-Bradley *et al.*, 1995), a Tolerable Intake for this endpoint has been developed on the basis of an effect level rather than a Benchmark Dose.[16] Calculation of a Tolerable Intake based upon the NOAEL for developmental effects in mice (i.e., 500 mg/kg-bw per day) divided by an uncertainty factor of 100 (×10 for interspecies variation, ×10 for intraspecies variation) results in a value of 5 mg/kg-bw per day. Parenthetically, derivation of a Tolerable Intake based upon division of a putative NOEL (150 mg/kg-bw per day) in this study (i.e., a significant increase in the incidence of only 1 of 27 skeletal malformations/variations — the occurrence of an extra 14th rib on the first lumbar arch — at the next highest dose of 500 mg/kg-bw per day) by an uncertainty factor of 100 (×10 for

[16] For comparison with the effect level, the BMD_{05} for the developmental effect that occurred at lowest dose in this study was approximately 140–245 mg/kg-bw per day; confidence in this value is low, though, due to lack of litter-specific data.

interspecies variation, ×10 for intraspecies variation) would yield a value of 1.5 mg/kg-bw per day. This is more than an order of magnitude higher than that based on the development of histopathological changes within the kidneys of male rats exposed for 16 weeks (Gaunt *et al.*, 1974).

3.3.3.2 Inhalation

Data available on tissue- or organ-specific toxicities associated with the inhalation of ethylene glycol following repeated exposure are limited to one short-term (intermittent) and one subchronic (continuous) study in which a limited range of endpoints was examined in rats, guinea pigs, rabbits, dogs and monkeys exposed (whole body) to ethylene glycol vapour (Coon *et al.*, 1970). In these investigations, reported adverse effects were not observed consistently, and results are considered inadequate as a basis for characterization of exposure–response for critical effects. Information from laboratory studies in humans limited to examination of a range of endpoints following relatively short-term exposures of a small number of volunteers is also considered inadequate as a basis for characterization of exposure–response (Wills *et al.*, 1974).

Developmental effects have been observed in rats and mice exposed via inhalation to ethylene glycol; however, interpretation is complicated somewhat by the possibility of significant additional intake via ingestion from grooming and/or percutaneous absorption in studies conducted using whole-body exposure (Tyl *et al.*, 1995a,b). However, the incidence of developmental effects was increased over that of a water aerosol-exposed control group at the highest concentration (2505 mg/m^3) in an investigation in which CD-1 mice were exposed nose-only for 6 hours per day on days 6 through 15 of gestation (Tyl *et al.*, 1995b). Based on examination of pelage washes in satellite groups, it was confirmed that deposition on the fur in surviving animals exposed at this concentration was considerably less than that in animals exposed via whole-body inhalation (Tyl *et al.*, 1995b). The estimated intake (assuming 60% absorption; Marshall and Cheng, 1983) of ethylene glycol, derived (Health Canada, 1994) on the basis of a putative NOAEL of 779 mg/m^3 from this study — approximately 156 mg/kg-bw per day[17] — is within the range reported for no-effect levels associated with the occurrence of developmental changes in mice administered the substance orally by gavage (Neeper-Bradley *et al.*, 1995) or the induction of histopathological changes in the kidneys of male rats receiving the substance in the diet (Gaunt *et al.*, 1974).

3.3.3.3 Dermal exposure

Repeated-dose toxicity studies in which the effects of ethylene glycol have been examined following direct dermal application in experimental species are insufficient to provide a meaningful basis for characterization of exposure–response. Indeed, they are limited to a single (poorly documented) chronic study in mice, in which analyses were restricted to gross examination of an unspecified range of organs and microscopic examination of gross lesions (Berenblum and Haran, 1955). In one developmental toxicity study, no effects upon fetal development were observed among pregnant CD-1 mice receiving a

[17] Based on theoretical maximum estimated intake through ingestion at the top dose, estimated intake at the NOAEL would be no greater than that via inhalation.

dermal application (covered) of a 50% aqueous solution of ethylene glycol for 6 hours per day on days 6 through 15 of gestation (NOAEL = 1700 mg/kg-bw per day) (Tyl *et al.*, 1995c). In this study, no effects on reproductive indices were observed following dermal exposure to up to 3500 mg ethylene glycol/kg-bw per day (Tyl *et al.*, 1995c). Based on available data, therefore, the Tolerable Intake developed for the induction of histopathological changes in the kidneys of male rats receiving the substance in the diet (Gaunt *et al.*, 1974) is likely protective for effects of ethylene glycol administered via the dermal route.

3.3.4 Uncertainties and recommendations

Based on very limited data, estimated total daily intakes of ethylene glycol from various media (i.e., ambient air, soil, food and consumer products) for different age groups in the vicinity of a point source or from consumer products for adults approach or exceed the Tolerable Intake.

For several age groups, estimated intake in air and soil in the vicinity of point sources slightly exceeds the Tolerable Intake. Estimated total daily intake is greatest for adults (the longest proportion of the lifespan) due to inclusion of upper-bounding estimates from consumer products for this subgroup of the population. Indeed, the single most important source of exposure to ethylene glycol for adults is via dermal exposure from consumer products. Based on estimated intake from polish/wax and tub and tile cleaner, the maximum estimated total daily intake of ethylene glycol in consumer products is 248.3 µg/kg-bw per day (i.e., 0.25 mg/kg-bw per day). However, it should be noted that this maximum reasonable worst-case estimate of total daily intake is based on assumptions of maximum concentrations of ethylene glycol in these products, 100% dermal absorption and standardized use scenarios, since the limitations of available data preclude further refinement with sufficient confidence. When based on the assumption that dermal absorption is proportional to the concentration of ethylene glycol in the product and that steady-state penetration occurs for periods equivalent to the average duration of product use in the standardized scenario, estimated daily intakes of ethylene glycol from the use of these products are several orders of magnitude lower. However, available data on permeability through human skin from product formulations are inadequate as a basis for confident estimation of exposure.

Confidence in the characterization of exposure of the general population in Canada to ethylene glycol is low owing principally to the lack of current representative monitoring data for air, drinking water, food and consumer products.

Limitations of the available data precluded development of estimates of the average daily intakes of ethylene glycol by the general population in Canada. Indeed, available data are inadequate even to indicate with confidence which environmental medium is the greatest source of exposure for the general population.

Confidence in the estimates of intake of ethylene glycol in ambient air by a subpopulation exposed due to its proximity to a source of discharge to the atmosphere is low, since these estimates are based on a predicted maximum daily average concentration at a fixed distance from the source and not

on measured concentrations. The frequency with which the predicted concentration in ambient air can occur is not reported, and there is no information concerning proximity to residences. Nevertheless, there is a moderate degree of certainty that the average daily intake by inhalation for the general population is much lower, since very few industrial point sources of discharge to the atmosphere are present in Canada and since the physical-chemical properties of ethylene glycol indicate a tendency to remain in water or soil if discharged to these media.

There is a high degree of certainty that the estimates of intake from ingestion of soil by a population exposed due to its proximity to a source of discharge to the atmosphere are upper bounding. Estimated intakes were based on the maximum reported concentration in soil, which was more than 30 times greater than the next highest value (i.e., 119 mg/kg versus 4290 mg/kg). Levels of ethylene glycol were less than the detection limit (5 mg/kg) in the remaining 97% of soil samples collected near the manufacturing plant.

Confidence in the estimates of intake by ingestion of foods is low, since the few available data are from earlier studies in other countries. There is a high degree of uncertainty regarding the extent of migration of ethylene glycol from RCF and PETE bottles currently used in Canada. Although ethylene glycol was present in all Italian wines sampled by Gaetano and Matta (1987), at a maximum concentration of 6.25 mg/L, the source of the ethylene glycol was not identified, and no other data concerning its presence in wine or other beverages were identified. Considerable additional uncertainty in the estimates of intake by ingestion of food arises from the assumption that the vast majority of foods consumed in Canada contain no ethylene glycol.

There is a high degree of uncertainty concerning exposure to ethylene glycol during use of various consumer products, related primarily to lack of information on the ranges and distributions of concentrations in any currently available consumer products in Canada. Indeed, the estimates presented herein may not be representative of the range of exposures of the general population to ethylene glycol in consumer products in Canada. For the few product classes considered, there is a reasonable degree of certainty that the estimates of intake by dermal absorption are upper bounding, since they are based on several conservative assumptions, including the maximum expected concentrations of ethylene glycol in these products and the assumption of complete dermal absorption. However, potential additional exposure through inhalation during use of these products has not been estimated.

The overall degree of confidence in the population exposure estimates is, therefore, low, owing principally to the lack of current representative monitoring data for air, drinking water, food and consumer products.

Available data are also inadequate to serve as a basis for quantitative estimation of exposure of passengers on aircraft to ethylene glycol during deicing operations.

Additional investigation of absorption through human skin from product formulations in assays where there has been attention to maintenance and characterization of viability would likely reduce uncertainty in the estimates of exposure for products.

The degree of confidence in the database on toxicity that serves as the basis for development of the Tolerable Intake for ethylene glycol is moderate. Although clinical and epidemiological data are inadequate to serve as a basis for characterization of exposure–response for critical effects, available data in humans are at least sufficient for crudely characterizing potential sensitivity relative to experimental species. However, additional characterization of the metabolic profile of ethylene glycol in humans through determination of metabolites in blood and urine would provide additional relevant information.

There is reasonable confidence that ethylene glycol is unlikely to be carcinogenic to humans, based on negative results in two species (mice and rats) and lack of genotoxicity in a limited number of identified *in vitro* and *in vivo* assays. This conclusion must be qualified to some extent, though, due to limitations of dose selection in the bioassay in rats, which reduced its sensitivity.

There is a moderately high degree of confidence that the critical effect of ethylene glycol relevant to long term exposure in the general environment is renal effects. This is based on their being observed at lowest concentrations in short-term and subchronic studies for which histopathological reporting was adequate in a relatively robust dataset in experimental animals and the observation of renal effects (including failure) in acute poisoning cases in humans. Confidence that the Tolerable Intake developed on the basis of renal effects is protective for other adverse effects of ethylene glycol such as teratogenicity is moderate. Indeed, should more extensive information become available to serve as the basis for estimation of exposure through consumer products, averaging time in relation to relevant endpoints needs to be considered additionally. Currently, estimates of intake in products, for example, have been averaged over a year, whereas for developmental/reproductive effects, peak exposures during product use may be a more appropriate basis for comparison.

The lack of data on progression of the renal lesions following chronic exposure in the most sensitive animal model examined to date is also a source of considerable uncertainty. This has been addressed in the development of the TI through application of an additional factor to account for less than chronic exposure. The potential impact of variations in diet on relative sensitivity to ethylene glycol associated renal lesions (i.e., calcium oxalate crystalluria and nephrosis) in the various strains of rats examined is also unknown. While the occurrence of "pneumonial changes" in the lungs and salivary adenitis are unlikely to impact on the toxicity of ethylene glycol in the critical study utilized as the basis of the TI, the occurrence of infection, a function primarily of the date of conduct of the study, is noted.

It should also be noted that while exposure-response for ethylene glycol induced renal lesions was best characterized in the 16 week study of Gaunt et al. (1974) which constituted the basis for the benchmark doses for the Tolerable Intake, the group sizes were small. However, the lower 95% confidence limit was only approximately 2 fold less than the central estimate of the benchmark dose (The latter was utilized in the calculation of the Tolerable Intake).

Rereading by a panel of pathologists of the slides in the Depass et al. (1986) study for which histopathological reporting of renal lesions is currently inadequate, may be desirable (if this is possible)

to provide additional quantitative data on dose-response for ethylene glycol-related lesions in another strain of rat. However, conduct of a chronic study in the strain examined in Gaunt et al. (1974) would more meaningfully reduce uncertainty.

With respect to human health, characterization of the ranges and distributions of concentrations of ethylene glycol in currently available consumer products in Canada and better characterization of exposure-response for renal effects in appropriate animal models in long term studies are clear priorities. It is also recommended that there be additional investigation of the magnitude of exposure of populations in the vicinity of industrial point sources.

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APPENDIX A: SEARCH STRATEGIES EMPLOYED FOR IDENTIFICATION OF RELEVANT DATA

Environmental characterization

Data relevant to the characterization of ethylene glycol were identified from existing review documents, published reference texts and on-line searches conducted between January and May 1996 of the following databases: Aqualine (1990–1996), ASFA (Aquatic Sciences and Fisheries Abstracts, Cambridge Scientific Abstracts; 1996), BIOSIS (Biosciences Information Services; 1990–1996), CAB (Commonwealth Agriculture Bureaux; 1990–1996), CESARS (Chemical Evaluation Search and Retrieval System, Ontario Ministry of the Environment and Michigan Department of Natural Resources; 1996), Chemical Abstracts (Chemical Abstracts Service, Columbus, Ohio; 1990–1996), CHRIS (Chemical Hazard Release Information System; 1964–1985), Current Contents (Institute for Scientific Information; 1990–1992, 1996), ELIAS (Environmental Library Integrated Automated System, Environment Canada library; January 1996), Enviroline (R.R. Bowker Publishing Co.; November 1995 – May 1996), Environmental Abstracts (1975 – February 1996), Environmental Bibliography (Environmental Studies Institute, International Academy at Santa Barbara; 1990–1996), GEOREF (Geo Reference Information System, American Geological Institute; 1990–1996), HSDB (Hazardous Substances Data Bank, U.S. National Library of Medicine; 1990–1996), Life Sciences (Cambridge Scientific Abstracts; 1990–1996), NTIS (National Technical Information Service, U.S. Department of Commerce; 1990–1996), Pollution Abstracts (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1996), POLTOX (Cambridge Scientific Abstracts, U.S. National Library of Medicine; 1990–1995), RTECS (Registry of Toxic Effects of Chemical Substances, U.S. National Institute for Occupational Safety and Health; 1996), Toxline (U.S. National Library of Medicine; 1990–1996), TRI93 (Toxic Chemical Release Inventory, U.S. Environmental Protection Agency, Office of Toxic Substances; 1993), USEPA-ASTER (Assessment Tools for the Evaluation of Risk, U.S. Environmental Protection Agency; up to December 21, 1994), WASTEINFO (Waste Management Information Bureau of the American Energy Agency; 1973 – September 1995) and Water Resources Abstracts (U.S. Geological Survey, U.S. Department of the Interior; 1990–1996). A survey of Canadian industry was carried out under authority of Section 16 of CEPA (Environment Canada, 1997b). Companies were required to supply information on uses, releases, environmental concentrations, effects or other data on ethylene glycol available to them if they met the trigger quantity of 1000 kg ethylene glycol per year. Reveal Alert was used to maintain an ongoing record of the current scientific literature pertaining to the potential environmental effects of ethylene glycol. Data obtained after October 1999 were not considered in this characterization.

Health characterization

Data relevant to the characterization of the potential risks of ethylene glycol to human health were identified through evaluation of existing review documents of the Environmental Criteria Assessment Office of the U.S. Environmental Protection Agency (U.S. EPA, 1987), the Agency for Toxic

Substances and Disease Registry of the U.S. Department of Health and Human Services (ATSDR, 1997) and the German Chemical Society (BUA, 1994), as well as reviews prepared under contract by BIBRA International (1996, 1998). A survey of Canadian industries was conducted under Section 16 of CEPA, in which companies were required to supply information concerning the use, release, environmental levels and toxicological effects of ethylene glycol. To identify additional relevant exposure and toxicological data, literature searches on ethylene glycol were conducted using the strategy of searching by its name or CAS registry number in the following databases: Canadian Research Index, CCRIS (Chemical Carcinogenesis Research Information System, U.S. National Cancer Institute), EMICBACK (backfile of Environmental Mutagen Information Center database, Oak Ridge National Laboratory), ETICBACK (backfile of Environmental Teratology Information Center database, U.S. Environmental Protection Agency and U.S. National Institute of Environmental Health Sciences), GENE-TOX (Genetic Toxicology, U.S. Environmental Protection Agency), HSDB, IRIS (Integrated Risk Information System, U.S. Environmental Protection Agency) and RTECS. Its name, registry number and major synonyms were searched in the CAB International, CISTIMON, Elias, EMBASE (1989–1999), Enviroline, Environmental Bibliography, Food Science and Technology Abstracts, Toxline (1980–1999), Medline (1985–1999), Microlog and Pollution Abstracts databases. Only relevant data acquired prior to January 2000 were considered in the determination of the effects of ethylene glycol on human health.

APPENDIX B: JUSTIFICATION FOR GENERIC DILUTION FACTORS

Introduction

Ethylene glycol is released to receiving water in various amounts. Whether or not any given scenario results in adverse effects on aquatic organisms depends upon a number of factors. Some of the key factors that determine whether a given release of ethylene glycol will be harmful to aquatic organisms are the following:

- the concentration of ethylene glycol in the final effluent (i.e., end-of-pipe),
- the dilution of the final effluent by the receiving water,
- the exposure concentration of ethylene glycol in the receiving water, and
- the length of time the organisms are exposed to ethylene glycol.

Effluents released to different types of water bodies undergo dilution to various degrees. In the absence of monitoring data downstream of discharge points, dilution of effluents is one element that is used for estimating a more realistic EEV. A generic and conservative dilution factor is used with supporting evidence presented below.

Dilution of effluents

Mixing of the effluent occurs in rivers, estuaries, lakes and sea to various degrees. Generally, rivers themselves are turbulent enough to allow for rapid mixing and dilution of the effluent. In small turbulent streams, complete mixing is likely to occur upon entry, provided the stream volume and flow are greater than the volume of effluent being discharged. In larger streams, the effluent may form a plume, and complete mixing may be reached only over a long distance.

When effluents are released to salt water, the effluents are usually of a lower density and float as a discrete layer on top of the salt water, where progressive mixing follows. In salt water, mixing results from diffusion and tidal currents.

Following an effluent release to a lake, there are additional physical factors to consider. Small, shallow lakes are subject to mixing due to wind-induced current; consequently, vertical stratification does not generally occur, except during late summer months. Even in a deeper, thermally stratified lake, effluents are likely to create a thermal turbulence and thus allow for some vertical mixing. Unlike streams, the water in lakes is more stationary, and, as a result, effluent may remain for a significant period of time. Therefore, impact near the discharge points could be higher if dispersion and mixing do not occur or are limited. A slowly moving lowland river can closely resemble a lake.

Dilution factors

Environment Canada recognizes that the dilution available for a given effluent discharged to any of the above water bodies is site and time specific. Dilution factors are known to vary by orders of magnitude (Holman, 1981; Rapaport, 1988). However, a generic and conservative dilution factor is used as a screening tool in the characterization of ethylene glycol for all types of water bodies at all sites.

The dilution factor used in this characterization is 10. A dilution of 1:10 means that the concentration of ethylene glycol in the effluent is diluted 10 times upon entering the receiving water body. Presented below are lines of evidence supporting that value.

Holman (1981) estimated the stream dilution factor (DF) (river flow/total effluent discharge rate) for municipal wastewater treatment plants (MWTPs) discharging into 161 major river basins in the United States. Based on mean stream flow conditions, the median stream dilution factor was 100, and 91% of the MWTP effluents discharged to surface water were diluted more than 10-fold. The author recommended that a DF of 10 be used for estimating conservative surface water concentrations for comparison with concentrations that cause adverse effects in aquatic systems.

In a study involving 11 675 MWTPs in the United States, Rapaport (1988) determined that greater than 95% of the MWTPs' discharge effluents were diluted more than 10-fold once released to streams. The dilution factors ((stream flow + plant flow)/plant flow) were calculated for mean river flow conditions.

Dilution factors are used in local exposure assessments for surface waters by many countries, including Germany, Finland, France, Japan, the Netherlands and the United Kingdom (OECD Secretariat, 1996). The dilution factors range from 10 to 1000 for river, lake, bay/estuary and ocean.

The European Centre for Ecotoxicology and Toxicology of Chemicals for the chemical industry uses a generic dilution factor of 10 in its local exposure models (ECETOC, 1994). Recently, the European Union has adopted a default dilution factor of 10 in its local exposure models for sewage from municipal treatment plants. This value is also used as a default dilution for other types of substances (EC, 1996).

In many Canadian provinces and U.S. states, point source effluent discharge objectives are calculated for the protection of aquatic life. These are derived by using a combination of methods, such as mixing zones, dilution factors and calculating the maximum quantity that can be discharged to a water body in a given period of time (B.C. Department of Lands, Forests and Water Resources, 1971; Dayton and Knight Ltd., 1993; OMEE, 1994; MEF, 1996). Dilution factors are calculated using low-flow conditions for the receiving rivers and streams. Low-flow conditions include 7Q2, 30Q 5, 7Q10 and 7Q20 (e.g., 7Q20 is the minimum 7-day average flow with a recurrence period of 20 years). For example, in Quebec, British Columbia, Yukon, Alberta, Northwest Territories and New Brunswick, minimum dilution factors of 100, 20, 20, 10, 10 and 8, respectively, are applied when deriving site-specific effluent discharge objectives for rivers and streams (B.C. Department of Lands, Forests and

Water Resources, 1971; Environment Canada, 1990; Dayton and Knight Ltd., 1993; MEF, 1996). In Ontario, initial mixing must have a minimum "near field" dilution ratio of 20:1 for the Great Lakes (OMEE, 1994).

Based on the above information, a dilution factor of 10 is considered sufficiently conservative to be used for estimating a more realistic EEV for all types of receiving water bodies. Thus, the EEV is obtained by dividing the final effluent end-of-pipe concentration of ethylene glycol by a factor of 10.

APPENDIX C: MANAGEMENT OF ETHYLENE GLYCOL AT CANADIAN AIRPORTS

Transport Canada has been the principal agency responsible for air transport in Canada and was responsible for initiating some monitoring of stormwater at international airports between 1970 and 1990. Monitoring during this period was infrequent, but, by 1990, all international airports in Canada had established stormwater monitoring programs (Transport Canada, 1995). Coinciding with the 1994 promulgation of a voluntary end-of-pipe discharge limit for glycol of 100 mg/L under CEPA, Transport Canada established a national program to sample and analyse airport effluent for glycols. Shortly thereafter, the Department of National Defence developed a similar program (Government of Canada, 1998).

At the present time in Canada, there are 726 certified airports, which range from large international airports to grass strips for landing small aircraft (Transport Canada, 1999a). The Canadian air transportation system is currently undergoing a major commercialization process initiated by the federal government. These changes could have an impact on future glycol management and monitoring. On July 13, 1994, the National Airports Policy (NAP) announced the transfer plans for 137 federally owned airports, including 26 airports under NAS, 71 regional/local airports, 31 small airports and 9 Arctic airports. Remote airports, which provide the only reliable year-round transportation link to isolated communities, will continue to be supported by the federal government (Transport Canada, 1999a). The 26 NAS airports (see Figure 5), which account for 94% of passenger and cargo traffic in Canada, include airports in provincial and territorial capitals, as well as any airport that handles at least 200 000 passengers per year (Transport Canada, 1999a). Under NAP, the federal government retains ownership of the 26 NAS airports and will lease them to Canadian Airport Authorities. These local operators are responsible for financial and operational management, while the federal government acts as landlord. For the regional and local airports, which serve scheduled passenger traffic, ownership is being offered to provincial and local governments, airport commissions, private businesses or other interests. Federal subsidies to these airports ceased March 31, 2000, unless exemptions were granted for special circumstances (Transport Canada, 1999a). The transfers of all NAS and other airports were to be completed by the end of fiscal year 1999/2000 (Transport Canada, 1999a).

Figure 5. Location of major airports under the National Airports System (NAS) in Canada (Transport Canada, 1999b)

As in the past, there will be no legislative requirement to continue GMPs and GOMPs. The plans provide a management control mechanism to ensure compliance with the CEPA guideline and the required actions to be taken when the guideline is not met. Exceedances of the guideline will be taken into account in the development of the plans for the following years (Simpson and Kent, 1999). ATAC plans to continue this exercise to maintain acceptable release levels of ethylene glycol and protect the local natural environment (Aalders, 1999). The plans identify the means of collecting, handling, storing, transporting and disposing of glycol-based fluids for each airport and also designate the areas in which deicing can take place and whether glycol recovery vehicles are required by the air carriers. Aircraft deicing is the air carriers' responsibility in terms of quantity, type and cost of containment, cleanup, storage and disposal. Airports and air carriers can manage glycols through a variety of ways, such as the use of vacuum trucks to collect the fluid on the apron, which can then be shipped off for recycling or treatment, and/or having underground piping and holding tanks to collect fluid immediately below the planes. Collected fluid may be diverted to sanitary sewer systems, storm sewer systems or tanker truck fill stations (MCIAA, 1997).

Transport Canada determines which airports require GMPs and which require GOMPs. Each identified airport must have a plan, which then must be approved by the airport general manager. Transport Canada will require a deicing/anti-icing licence if the plan requirements are not met (Transport Canada, 1999c). The GMPs and GOMPs are updated on an annual basis and, together with the regular monitoring of stormwater effluent during the deicing season, are designed with the objective that all airports currently operated by Transport Canada are compliant with the CEPA guidelines (Transport Canada, 1997c). The 26 NAS airports will remain on federal lands and therefore will still be subject to the CEPA Part IV glycol discharge guideline and the requirements under the *Fisheries Act*. Under

CEPA Part IV, a total glycol discharge limit of 100 mg/L prior to release into receiving waters has been established for the protection of the environment and is used when designing and implementing the management of aircraft anti-icing and deicing activities (Canada Gazette, 1994). In addition, the Canadian water quality guideline for ethylene glycol has been prepared by the Task Force on Water Quality Guidelines for the CCME and set at a level of 192 mg/L for the protection of freshwater aquatic life. A related 5-day BOD effluent quality and wastewater treatment guideline was set at 20 mg/L for stormwater samples at federal establishments in 1976 (Environment Canada, 1976a). The above guidelines are not regulated values; however, the effects of ethylene glycol release can be measured against Sections 35 and 36 of the *Fisheries Act*, which deal with the destruction of fish passageways, alteration of fish habitat and deposition of substances deleterious to fish. Violations of these sections of the Act can result in penalties and fines when enforced.

Although most airports report releases of "total glycol," by far the vast majority of glycol used in Canada for aircraft anti-icing/deicing is ethylene glycol (Leroux, 1999). Propylene glycol, the other glycol used for this purpose in Canada, is reported to be used only minimally at Hamilton Airport, Moncton Airport, Vancouver International Airport and Winnipeg International Airport and by Federal Express air carriers (MacCallum, 1998; Moncton Airport, 1999; Thaler, 1999).

Table 1. Chemical and physical properties of ethylene glycol

Property	Parameter	Reference	Property value input parameters (Shirley *et al*, 1995)
Molecular formula	$C_2H_6O_2$		
Molecular weight (g/mol)	62.07		62.07
CAS registry number	107-21-1		
Common synonyms	glycol, glycol alcohol, ethylene alcohol, ethylene dihydrate, monoethylene glycol, 1,2-dihydroxyethane, 1,2-ethanediol		
Physical state (25°C)	colourless liquid		
Melting point (°C)	–13 –11.5	Budavari *et al*, 1989; Howard, 1990 Weast, 1982–1983; IPCS, 1993; HSDB, 1999	–13
Boiling point (°C)	197.6	Budavari *et al*, 1989; Howard, 1990; IPCS, 1993; HSDB, 1999	
Density (g/mL) at 20° C	1.1135 1.1 1.1088 1.1130	Budavari *et al*, 1989 IPCS, 1993 HSDB, 1999 Verschueren, 1983	
Vapour pressure (Pa)	6.7 (20°C) 7 (20°C) 12.27 (5°C) 11.7 (25°C)	Verschueren, 1983 IPCS, 1993 Howard, 1990 HSDB, 1999	12
Henry's law constant ($Pa \cdot m^3/mol$)	6.08×10^{3} 5.81×10^{6} (calculated) 2.37×10^{5} (calculated) 6.0×10^{3} (experimental)	Howard, 1990 Hine and Mookerjee, 1975 Hine and Mookerjee, 1975 Hine and Mookerjee, 1975	7.5×10^{3} (calculated based on fictitious water solubility of 1.0×10^{5})
Log K_{ow}	–1.36 –1.93 –2.02	Howard, 1990 Verschueren, 1983 Iwase *et al*, 1985	–1.36
Solubility in water	miscible	Budavari *et al*, 1989; IPCS, 1993	1.0×10^{11} mg/L
Conversion factor	multiply by 1.11 g/mL to convert µL/L to mg/L		
Half-life — air	0.35–3.5 days 0.24–2.4 hours	Howard *et al*, 1991 Darnall *et al*, 1976	55 hours
Half-life — water	2–12 days (aerobic) 8–48 days (anaerobic)	Howard *et al*, 1991 Howard *et al*, 1991	55 hours
Half-life — groundwater	4–24 days	Howard *et al*, 1991	
Half-life — soil	2–12 days	Howard *et al*, 1991	55 hours
Half-life — sediment	–	–	170 hours
Half-life —	–	–	55 hours

[illegible]	[illegible]	[illegible]	[illegible]
suspended sediment			
Half-life — fish	1–1.5 days	Abdelghani *et al*, 1990	24 hours
Half-life — aerosol	–	–	24 hours

Table 2. Estimate of quantities of ethylene glycol released, by compartment (NPRI, 1995, 1996)

Compartment	Amount released (tonnes)	
	1995	1996
Air	537	504
Water	68	69
Land	3254	3210
Underground injection	564	384
Total releases	4423	4167

Table 3. Concentrations of ethylene glycol sampled at selected monitoring stations of Canadian airports for the 1997/98 and 1998/99 deicing seasons

Airport	[illegible]	Number of samples	Detection limit[1] (mg/L)	Median[2] (mg/L)	Mean[2] (mg/L)	Maximum[2] (mg/L)	Reference
Baie Comeau	30 Mar 98	2	–	–	5	5	Transport Canada, 1999d
Calgary International	15 Oct 97 – 27 May 98	9	2	<DL	14	112	Richmond, 1999
	26 Oct 98 – 27 May 99	7	2	<DL	<DL	<DL	CAA, 1999
Charlottetown	23 Oct 97 – 1 May 98	2	5	<DL	<DL	<DL	Transport Canada, 1998a
	15 Feb 99	1	5	–	–	<DL	Transport Canada, 1999d
Chevery	4 May 98 – 6 May 98	3	2	–	<DL	<DL	Transport Canada, 1998a
Edmonton International	7 Apr 98	1	10	–	–	<DL	ERAA, 1999
	29 Sep 98 – 23 Oct 98	4	10	<DL	23	60	ERAA, 1999
Fredericton	14 Jan 98 – 25 Mar 98	5	4.5	5	6	10	Transport Canada, 1998a

Airport	[illegible]	Number of samples	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	13 Jan 99 – 19 Jan 99	4	5	<DL	<DL	<DL	Transport Canada, 1999d
Gander International	29 Apr 98	4	5	<DL	25	84	Transport Canada, 1998a
	17 Dec 98 – 28 Apr 99	12	5	25	95	820	Transport Canada, 1999d
Halifax International	17 Nov 97 – 21 Apr 98	62	5	6	17	190	HAA, 1999
	16 Oct 98 – 14 Apr 99	48	5	6	13	77	Transport Canada, 1999d
Iles de la Madeleine	22 Nov 98 – 13 Apr 99	8	2	<DL	3	5	Transport Canada, 1999d
Kelowna	7 Oct 98 – 22 Apr 99	96	5	<DL	11	180	Transport Canada, 1999d
London	28 Oct 97 – 26 May 98	35	4	<DL	<DL	<DL	Transport Canada, 1998a
Mont-Joli	12 Apr 99 – 15 Apr 99	6	2	<DL	<DL	<DL	Transport Canada, 1999d
Montreal International — Dorval	13 Nov 97– 25 May 98	71	1	13	92	3700	Aéroports de Montréal, 1998
	4 Oct 98 – 31 May 99	52	1	16	24	182	Aéroports de Montréal, 1999
Montreal International — Mirabel	17 Dec 97 – 12 May 98	120	5	<DL	39	635	Aéroports de Montréal, 1998
	21 Dec 98 – 3 May 99	88	6	13	17	106	Aéroports de Montréal, 1999
North Bay	27 Oct 97 – 27 May 98	58	4	<DL	9	190	Transport Canada, 1998a
Ottawa Macdonald-Cartier International	27 Oct 97 – 13 Mar 98	79	2	<DL	12	222	MCIAA, 1998
	26 Oct 98– 8 Apr 99	142	2	<DL	24	226	MCIAA, 1999
Prince George	8 Apr 98	1	71	–	–	71	Transport Canada, 1998a
	18 Nov 98 – 4 May 99	24	5	<DL	196	2220	Transport Canada, 1999d
Québec Jean Lesage International	21 Oct 97 – 31 Mar 98	48	1	11	9	80	Transport Canada, 1998a
	20 Nov 98 – 19 Apr 99	110	2	4	74	4700	Transport Canada, 1999d
Regina	29 Oct 97 – 24 Mar 98	5	5	<DL	<DL	<DL	Transport Canada, 1998a
	6 Oct 98 – 26 Apr 99	30	5	<DL	<DL	<DL	RAA, 1999
Sault Ste. Marie	27 Oct 97 – 20 May 98	45	4	<DL	<DL	7	Transport Canada, 1998a
St. John's Newfoundland	18 Dec 97 – 28 Apr 98	17	5	<DL	15	80	Transport Canada, 1998a

Airport	Sampling dates within deicing season	Number of samples	Detection limit[1] (mg/L)	[illegible] (mg/L)	[illegible] (mg/L)	[illegible] (mg/L)	Reference
	15 Jan 99 – 10 May 99	140	5	12	28	170	Transport Canada, 1999d
Saint John New Brunswick	30 Dec 97– 10 Mar 98	5	5	10	43	105	SJAA, 1998
	27 Nov 98 – 12 Mar 99	5	5	50	48	80	SJAA, 1999
Sept-Iles	11 Mar 99 – 3 May 99	5	2	2	6	20	Transport Canada, 1999d
Sudbury	29 Oct 97 – 4 Mar 98	6	2	39	411	2320	Transport Canada, 1998a
Terrace	19 Feb 99 – 29 Mar 99	28	5	<DL	<DL	17	Transport Canada, 1999d
Thunder Bay	15 Oct 97 – 22 Apr 98	24	1	<DL	2	31	TBIAA, 1998
	6 Oct 98 – 28 Apr 99	22	1	<DL	<DL	<DL	TBIAA, 1999
Timmins	30 Mar 98 – 28 May 98	9	5	<DL	73	413	Transport Canada, 1998a
	30 Mar 99 – 11 May 99	6	4	<DL	46	245	Transport Canada, 1999d
Toronto Lester B. Pearson International	1 Oct 97 – 30 Apr 98	517	2	4	25	348	GTAA, 1998
	6 Oct 98 – 30 Apr 99	472	4	<DL	14	200	GTAA, 1999
Val d'Or	3 Apr 98 – 15 Apr 98	10	2	<DL	3	10	Transport Canada, 1998a
	2 Dec 98 – 13 Apr 99	3	2	-	<DL	<DL	Transport Canada, 1999d
Vancouver International	29 Oct 97 – 1 Apr 98	201	3	<DL	4	84	VIAA, 1998
	28 Oct 98 – 28 Apr 99	242	3	<DL	5	120	VIAA, 1999
Windsor	5 Nov 97 – 19 Apr 98	41	5	<DL	<DL	7	Transport Canada, 1998a
	2 Nov 98 – 19 May 99	47	5	<DL	<DL	7	Transport Canada, 1999d
Winnipeg International	2 Oct 97 – 26 May 98	180	2 and 10	10	11	110	North/South Consultants Inc., 1998
	8 Apr 99 – 31 May 99	60	2 and 10	10	12	70	North/South Consultants Inc., 1999

[1] Detection limit (DL) equivalent to minimum values in all cases (except Gander 1998/99 season: minimum equivalent to 6 mg/L).

[2] For calculation of summary statistics, a concentration equal to the limit of detection was assumed for samples in which glycols were not detected. Where detection limits were not indicated and concentrations were recorded as "<X," a detection limit equal to "X" was assumed. Median values were not calculated for data sets having fewer than four samples.

Note: For many airports, "total glycol" values have been reported; however, none of the airports listed above used other glycols during the two deicing seasons indicated (Winnipeg and Vancouver International Airports are the only exceptions, but data were reported in terms of ethylene glycol).

Table 4. Summary statistics of concentrations of ethylene glycol in stormwater of Canadian airports

Deicing season	Number of samples	Summary statistics and percentiles of distribution of measured concentrations (mg/L)						
		Mean	Median	75th	90th	95th	99th	Maximum
1996/97	1395	108	5	54	255	541	1780	6900
1997/98	1606	22	4	10	38	80	256	3700
1998/99	1676	23	5	12	45	65	180	4700
1997–99 (only) combined	**3282**	**23**	**5**	**10**	**42**	**72**	**200**	**4700**

Table 5. Concentration of ethylene glycol in groundwater sampled at Canadian airports[1]

Airport	Sampling dates	Number of samples	Detection limit (mg/L)	Median (mg/L)	Mean (mg/L)	Maximum (mg/L)	Reference
Calgary International	4 Oct 96 – 28 Jul 99	17	2	<DL	4	38	Calgary Airport Authority, 1998
Charlottetown	23 Oct 96 – 1 May 98	7	5	<DL	<DL	<DL	Transport Canada, 1997d, 1998c
Montreal International —Dorval	13 Nov 97 – 25 May 98	20	0.5	1.3	8	42	Aéroports de Montréal, 1998
Montreal International —Mrabel	28 Nov 97 – 6 Jul 99	5	6	<DL	<DL	39	Aéroports de Montréal, 1999
Ottawa Macdonald-Cartier International	Dec 85 – Dec 86	?	5	<DL	<DL	415	Transport Canada, 1987

[1] For many airports, "total glycol" values have been reported; however, none of the airports listed used other glycols. All samples taken in the immediate vicinity of deicing operations and at shallow depth were excluded. Detection limit (DL) equivalent to minimum values in all cases.

Table 6. Deterministic estimates of upper-bounding daily intakes for adults by dermal absorption from consumer products[1]

Consumer product	Maximum concentration of ethylene glycol in product	Event description	Event frequency (per year)	Exposed skin area (cm^2)[2]	Estimated maximum average daily intake[3] (µg/kg-bw per day)
Latex paint	5% (Environment Canada, 1997b)	roller application to walls and ceiling of an average-sized room[4]	1.4[7]	220	7.2
Floor polish/wax	3.5% (U.S. EPA, 1986)	manual application of undiluted product to an average-sized floor with a rag or sponge[5]	4[8]	400	4.6
Auto polish/wax	0.03% (U.S. EPA, 1986)	manual application to an automobile with a sponge-like foam pad[6]	6[9]	400	0.09
Tub and tile cleaner	3% (Flick, 1986)	manual application to bathroom sink and bathtub[5]	156[10]	400	180.8
		manual application to tiled wall in bathroom or elsewhere[5]	48[10]	400	55.6
		total estimated intake from tub and tile cleaner			236.4

1 These estimates are based on *Standard scenarios for estimating exposure to chemical substances during use of consumer products* (U.S. EPA, 1986). It is assumed that thin films of liquid products form on the exposed skin surface and that complete dermal absorption of ethylene glycol present in the thin films occurs.

2 Estimates of areas of exposed skin are from U.S. EPA (1986). An area of 220 cm^2 is approximately 10% of the surface area of the face, hands and forearms. An area of 400 cm^2 is approximately the combined area of the palms and outstretched fingers of two adult hands.

3 Reasonable worst-case daily intakes are based on the assumption of complete dermal absorption of ethylene glycol present in thin films contacting the skin. Minimum average daily intakes based on penetration rates that are proportional to the ethylene glycol content of the products are several orders of magnitude less for each of these products (Health Canada, 2000).

4 Assuming a resulting film thickness on the hands of 0.0098 cm (U.S. EPA, 1986).

5 Assuming a resulting film thickness on the hands of 0.0021 cm (U.S. EPA, 1986).

6 Assuming a resulting film thickness on the hands of 0.0032 cm (U.S. EPA, 1986).

7 U.S. EPA (1986) indicates that 7 events per year is the 95th percentile number of rooms painted of the 20% of respondents painting during the survey year. This value pertains to the year in which the activity is performed. If it is assumed that each room is painted every 5 years (U.S. EPA, 1986), the event frequency is 7 per year.

8 It is not indicated whether this is a mid-point or upper-percentile estimate of event frequency (U.S. EPA, 1986).

9 This is a conservative estimate, based on the assumption that 5.4% of the U.S. population used automotive wax 6 or more times per year (U.S. EPA, 1986).

10 Based on average event frequencies from U.S. EPA (1997).

Table 7. Summary statistics of maximum stormwater effluent concentrations of ethylene glycol measured at individual airports for months of March and April from 1996 to 1999

Deicing season	Number of airports	Summary statistics and percentiles of distribution of measured concentrations (mg/L)				
		Mean maximum	Highest maximum	50th	95th	99th
1997/98	24	131	1360	42	404	1142
1998/99	23	332	4700	50	1627	4058
1997–1999	**47**	**229**	**4700**	**43**	**1076**	**3357**

Table 8. Direct toxicity risk quotients for exposure of algae to ethylene glycol

Effluent concentration (mg/L)	Descriptor	EEV in receiving water (mg/L)	Quotient[1]
4700	highest maximum — 1997–1999 seasons (Table 4)	470	0.72
1076	95th percentile — spring maxima 1997–1999 (Table 7)	108	0.17
200	99th percentile — all data, 1997–1999 (Table 4)	20	0.03
100	CEPA Part IV guideline	10	0.02

[1] Quotient is derived by dividing the EEV by the ENEV (654 mg/L).

Table 9. Direct toxicity risk quotients for exposure of amphibians to ethylene glycol

Effluent concentration (mg/L)	Descriptor	EEV in receiving water (mg/L)	Quotient[1]
4700	highest maximum — 1997–1999 seasons (Table 4)	470	0.99
1076	95th percentile — spring maxima 1997–1999 (Table 7)	108	0.23
200	99th percentile — all data, 1997–1999 (Table 4)	20	0.04
100	CEPA Part IV guideline	10	0.02

[1] Quotient is derived by dividing the EEV by the ENEV (473 mg/L).

Table 10. Canadian water quality guidelines for dissolved oxygen (CCME, 1999)

Freshwater ecosystem	Guideline value (mg/L)	
	Early life stages	Other life stages
Warm-water fish	6.0	5.5
Cold-water fish	9.5	6.5

Table 11. Indirect toxicity risk quotients for exposure of aquatic biota to ethylene glycol

Effluent concentration (mg/L)	Descriptor	EEV in receiving water (mg/L)	Oxygen deficit[1] (mg/L)	Quotient[2]
4700	highest maximum — 1997–1999 seasons (Table 4)	470	57.9	16.1
1076	95th percentile — spring maxima 1997–1999 (Table 7)	108	13.8	3.8
200	99th percentile — all data, 1997–1999 (Table 4)	20	3.1	0.86
100	CEPA Part IV guideline	10	1.9	0.53

[1] Oxygen deficit is the application of the Streeter and Phelps (1925) oxygen sag model to provide the number of mg O_2/L below the saturation point of 13.1 mg O_2/L and resulting from the assumed EEV in the receiving water.
[2] The quotient represents the ratio between the calculated oxygen deficit and the minimal oxygen deficit of 3.6 mg/L needed to meet the cold-water CCME freshwater guideline of 9.5 mg/L, assuming a water temperature of 4°C.

Table 12. Deterministic estimates of worst-case daily intakes of ethylene glycol for a highly exposed population in the immediate vicinity of an industrial point source

Route of exposure	Intakes of ethylene glycol for various age groups in the exposed population (µg/kg-bw per day)					
	0–6 months[1]	7 months – 4 years[2]	5–11 years[3]	12–19 years[4]	20–59 years[5]	60+ years[6]
Inhalation[7]	28	60	47	27	23	20
Ingestion of soil[8]	17	28	9	2	2	2
Total daily intake	45	88	56	29	25	22

[1] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 of air per day and to ingest 30 mg of soil per day (EHD, 1998).
[2] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 of air per day and to ingest 100 mg of soil per day (EHD, 1998).
[3] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 of air per day and to ingest 65 mg of soil per day (EHD, 1998).
[4] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 of air per day and to ingest 30 mg of soil per day (EHD, 1998).
[5] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 of air per day and to ingest 30 mg of soil per day (EHD, 1998).
[6] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 of air per day and to ingest 30 mg of soil per day.(EHD, 1998).
[7] Based on the maximum daily average concentration (100 µg/m^3) predicted in ambient air at ground level at a distance of 1.8 km from the facility perimeter of an industrial point source of discharge to the atmosphere (Environment Canada, 1997b). The same concentration is assumed for indoor air.
[8] Based on the maximum reported concentration (4290 mg/kg) in soil near an industrial point source of discharge (AEP, 1996).

Table 13. Deterministic estimates of reasonable worst-case daily intakes of ethylene glycol from ingestion of foods

Food item	Intakes of ethylene glycol for various age groups in the general population (µg/kg-bw per day)					
	0–6 months[1]	7 months – 4 years[2]	5–11 years[3]	12–19 years[4]	20–59 years[5]	60+ years[6]
Cake[7]	0.3	19.4	27.8	23.6	10.7	7.9
Pie, other[8]	1.0	2.4	3.3	1.8	1.7	1.6
Candy, other[9]	1.1	11.8	9.2	5.9	2.5	1.7
Soft drinks[10]	<0.1	0.7	0.6	0.4	0.2	0.1
Wine[11]	–	<0.1	0.1	0.2	1.6	1.0
Total daily intake[12]	<2.5	<34.4	41.0	31.9	16.7	12.3

1 Assumed to weigh 7.5 kg and to consume food items at average daily rates indicated in EHD (1998).

2 Assumed to weigh 15.5 kg and to consume food items at average daily rates indicated in EHD (1998).

3 Assumed to weigh 31.0 kg and to consume food items at average daily rates indicated in EHD (1998).

4 Assumed to weigh 59.4 kg and to consume food items at average daily rates indicated in EHD (1998).

5 Assumed to weigh 70.9 kg and to consume food items at average daily rates indicated in EHD (1998).

6 Assumed to weigh 72.0 kg and to consume food items at average daily rates indicated in EHD (1998).

7 Assumed to contain ethylene glycol due to contact with RCF. Based on a maximum reported concentration of 34 mg/kg in fruit cake in the U.K. (Castle *et al*, 1988).

8 Assumed to contain ethylene glycol due to contact with RCF. Based on the limit of detection (10 mg/kg) for analysis of meat pies in the U.K. (Castle *et al*, 1988).

9 Assumed to contain ethylene glycol due to contact with RCF. Based on a maximum reported concentration of 34 mg/kg in boiled sweets in the U.K. (Castle *et al*, 1988).

10 Assumed to contain ethylene glycol due to migration from PETE bottles. Based on a maximum reported concentration of 0.104 mg/L in 3% acetic acid (used to simulate carbonated beverages) following storage for 6 months at 32°C (Kashtock and Breder, 1980).

11 Based on the maximum reported concentration (6.25 mg/L) of ethylene glycol in wine in Italy (Gaetano and Matta, 1987).

12 It is assumed that there are no daily intakes of ethylene glycol from the remaining 176 food items for which daily rates of consumption are available in EHD (1988), since no data are available concerning concentrations of ethylene glycol in these food items.

Table 14. Incidence of renal lesions in male rats administered ethylene glycol for 2 years[1]

	Dose of ethylene glycol (mg/kg-bw per day)				
	0 (A)	0 (B)	40	200	1000
Incidence of calcium oxalate crystalluria in male rats					
Incidence at 6-month interim sacrifice (Snellings, 2000)	0/10	0/10	0/10	0/10	6/10
Incidence at 12-month interim sacrifice (Snellings, 2000)	0/10	0/10	0/10	0/10	10/10
Overall incidence reported in DePass *et al.* (1986a)	0/128	0/128	0/129	0/129	16/116 ($p < 0.001$)
Incidence of tubular hyperplasia in male rats					
Incidence at 6-month interim sacrifice (Snellings, 2000)	1/10	3/10	2/10	2/10	10/10
Incidence at 12-month interim sacrifice (Snellings, 2000)	9/10	8/10	8/10	8/10	0/10
Overall incidence reported in DePass *et al.* (1986a)	10/128	11/128	10/129	10/129	10/116
Incidence of tubular dilation in male rats					
Incidence at 6-month interim sacrifice (Snellings, 2000)	0/10	0/10	0/10	1/10	10/10
Overall incidence reported in DePass *et al.* (1986a)	0/128	0/128	0/129	1/129	10/116 ($p < 0.001$)
Incidence of peritubular nephritis in male rats					
Incidence at 6-month interim sacrifice (Snellings, 2000)	0/10	0/10	0/10	0/10	6/10
Incidence at 12-month interim sacrifice (Snellings, 2000)	2/10	4/10	4/10	7/10	0/10
Overall incidence reported in DePass *et al.* (1986a)	2/128	4/128	4/129	7/129	6/116
Incidence of oxalate nephrosis in male rats					
Incidence in animals dead or sacrificed when moribund (Snellings, 2000)	0/19	0/18	0/19	0/16	95/96
Overall incidence reported in DePass *et al.* (1986a)	0/128	0/128	0/129	0/129	95/116 ($p < 0.001$)
Incidence of hydronephrosis in male rats					
Incidence (unilateral) at 6-month interim sacrifice (Snellings, 2000)	0/10	0/10	0/10	0/10	1/10
Incidence at 24-month sacrifice (Snellings, 2000)	1/69	1/70	0/70	0/17	no data
Incidence in animals dead or sacrificed when moribund (Snellings, 2000)	0/19	3/18	0/19	3/16	71/96
Overall incidence reported in DePass *et al.* (1986a)	1/128	4/128	0/129	3/129	72/116 ($p < 0.001$)
Incidence of glomerulonephrosis in male rats					

Incidence at 18-month sacrifice (Snellings, 2000)	20/20	19/20	20/20	20/20	no data
Incidence at 24-month sacrifice (Snellings, 2000)	69/69	70/70	70/70	73/73	no data
Incidence in animals dead or sacrificed when moribund (Snellings, 2000)	17/19	17/18	13/19	14/16	5/96
Overall incidence reported in DePass *et al.* (1986a)	106/128	106/128	103/129	107/129	5/116

[1] The incidence of ethylene-glycol induced renal lesions has been verified from the pathology reports on individual animals (Brantom, 2000b).

Table 15. Benchmark Doses (BMD_{05}s) for effects on the kidney in male rats[1] (Gaunt *et al.*, 1974)

Renal histopathology	BMD_{05} (mg/kg-bw per day)	95% LCL on BMD_{05} (mg/kg-bw per day)	p-value	Chi-square	df	Degree of polynomial
Incidence of individual nephrons with degenerative changes: 0/15, 1/15, 1/15, 2/15 and 5/15 ($p < 0.05$)	83.8	45.1	0.86	0.74	3	4
Incidence of individual nephrons with degenerative changes and occasional oxalate crystal: 0/15, 0/15, 0/15, 1/15 and 4/15 ($p < 0.05$)	217.6	75.4	0.75	0.59	2	4
Incidence of several nephrons with degenerative changes and frequent crystals: 0/15, 0/15, 0/15, 0/15 and 2/15	553.9	180.1	0.99	0	3	4
Incidence of generalized tubular damage and heavy crystals: 0/15, 0/15, 0/15, 0/15 and 4/15 ($p < 0.05$)	465.5	158.1	0.99	0.02	3	4
Total animals with tubular damage: 0/15, 1/15, 1/15, 4/15 ($p < 0.05$) and 15/15 ($p < 0.01$)	48.6	21.5	0.62	0.94	2	4

[1] Male Wistar rats were administered ethylene glycol in the diet for 16 weeks at doses of 0, 35, 71, 180 or 715 mg/kg-bw per day (Gaunt *et al*, 1974).

Table 16. Additional analyses of Benchmark Doses for renal effects in rats[1]

Renal histopathology	BMD_{05} (mg/kg-bw per day)	95% LCL on BMD_{05} (mg/kg-bw per day)	p-value	Chi-square	df	Degree of polynomial
Incidence of tubular dilation: 0/10, 0/10, 0/10, 5/10 and 8/9	316.4	85.5	0.12	4.25	2	4
Incidence of tubular degeneration: 0/10, 0/10, 0/10, 5/10 and 9/9	501.9	214.9	0.96	0.26	3	4
Incidence of intratubular crystals: 0/10, 0/10, 0/10, 3/10 and 8/9	453.7	145	0.75	1.2	3	4

[1] Male Sprague-Dawley rats were administered ethylene glycol in drinking water for 90 days at doses of 0, 205, 410, 950 or 3130 mg/kg-bw per day (Robinson *et al*, 1990).

[2] Incidences for the two (0 dose) control groups (A and B) were combined.